"CORRECTED TIMI FRAME COUNT IN CORONARY SLOW FLOW PHENOMENON" A SHORT-TERM FOLLOW-UP STUDY

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CERTIFICATE

This is to certify that the dissertation entitled **"CORRECTED TIMI FRAME COUNT IN CORONARY SLOW FLOW PHENOMENON" A SHORT-TERM FOLLOW-UP STUDY** is the bonafide original work of **Dr.MOHAMED MUTHIULLAH**, in partial fulfillment of the requirements for D.M. Branch-II (CARDIOLOGY) examination of THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY to be held in August 2007.The period of post-graduate study and training was from August 2004 to July 2007.

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DECLARATION

I **Dr.MOHAMED MUTHIULLAH,**solemnly declare that this dissertation entitled, **"CORRECTED TIMI FRAME COUNT IN CORONARY SLOW FLOW PHENOMENON" A SHORT-TERM FOLLOW-UP STUDY** is bonafide work done by me at the department of Cardiology,Madras Medical College and Government General Hospital during the period 2004 – 2007 under the guidance and supervision of the Professor and Head of the department of Cardiology of Madras Medical College and Government General Hospital,Professor V.Jaganathan M.D.D.M.This dissertation is submitted to The Tamil Nadu Dr.M.G.R Medical university,towards partial fulfillment of requirement for the award of **D.M. Degree (Branch-II) in Cardiology.**

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"learn to heal"

INTRODUCTION

AN APPROACH TO THE PATIENT WITH NON OBSTRUCTIVE CORONARY ARTERY DISEASE

Patients with Non Obstructive Coronary Artery Disease (NOCAD) utilize a significant part of our health care resources. Their diagnosis and treatment can often be difficult and time consuming.A simple classification system and stepwise diagnostic approach may help to reduce unnecessary testing. Also, utilization of a chest pain clinic may be beneficial for these patients.

Chest pain results in over 5 million visits to emergency departments, 2 million admissions, and multiple out patient consultations every year all over the world.A large number of these patients will eventually undergo coronary angiography and depending on the population studied, a significant number (20% to 30%) will have normal- appearing coronary arteries.Indeed, 10% to 15% of all patients undergoing angiography in the catheterization laboratory have normal coronary arteries.[1]

The treatment and diagnosis of chest pain in patients with NOCAD continues to represent a major challenge to contemporary cardiology. When evaluating these patients, a revisit of the history and physical examination helps to narrow the extensive list of pathologic conditions in the differential diagnosis and focus further investigation. It is important to develop a logical, step-wise approach so as to limit unnecessary testing, expense, and patient discomfort.[1]

The evaluation of patients with chest pain and NOCAD should allow classification of patients into 1 of 3 main groups.

The first group includes patients with chest pain and a flow-limiting coronary lesion undetectable on routine angiography studies but may be detected after physiologic evaluation.

The second group includes patients without significant atherosclerotic epicardial disease, but with evidence of epicardial flow or microvascular reactivity abnormalities that may lead to myocardial ischemia.

The third group consists of patients without evidence of epicardial or microvascular abnormalities after extensive coronary and physiologic assessment. This group will need further evaluation and assessment for a noncoronary or noncardiac etiology.

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G. Drug-induced (Cocaine)

H. Enhanced pain perception/psychogenic

Epicardial Atherosclerotic Cause for Ischemia

It should be emphasized that physiologically significant coronary stenosis may not be readily apparent on angiography. A review of the angiogram and/or further assessment with fractional flow reserve(FFR) or intravascular ultrasound(IVUS) may be necessary to ensure there is no significant epicardial coronary lesion.

Epicardial or Microvascular Cause for Ischemia

Once a flow-limiting lesion has been ruled out as a contributing factor for chest pain, other coronary abnormalities must be considered, including epicardial spasm, myocardial bridging, coronary dissection,epicardial slow flow or abnormalities in the microvasculature.Myocardial bridging and dissection should be readily apparent on the angiogram; however, epicardial vasoconstriction and abnormalities of the microvasculature will require further investigative and provocative procedures.

Epicardial Coronary Spasm

Epicardial coronary spasm was first described by Prinzmetal in 1959 and although relatively rare,should be considered in all patients with chest pain and NOCAD.It affects approximately 4 out of

100,000 people (approximately 2% of patients complaining of angina).The epicardial coronary arteries can exhibit significant vasoactivity and patients with or without coronary atherosclerosis may have spontaneous increases in coronary vasomotor tone, resulting in myocardial ischemia.

Patients often complain of nocturnal or early morning chest pain that typically occurs at rest and less so with exertion. In fact, they often maintain good exercise tolerance.

This atypical presentation of epicardial spasm may lead to chest pain symptoms being erroneously dismissed as organic. Certain triggers can exacerbate coronary spasm, such as exposure to cold, emotional stress, alcohol, vasoconstricting medications, cocaine, or tobacco, and these should be avoided. Furthermore, coronary vasospasm can lead to cardiac arrhythmias, including ventricular tachycardia/fibrillation,heart block, acute infarction, or sudden death.

The clinical history aids in the diagnosis of coronary vasospasm and noninvasive modalities such as ambulatory Holter monitoring, documenting ST-segment elevation, or provocative echocardiography have been used in diagnosing vasospasm.If noninvasive testing is equivocal, then provocative testing with methylergonovine often demonstrates the presence of coronary spasm in these patients.Although normal vasoconstriction can result in as much as a 20% change in lumen diameter, coronary spasm is considered to be present when a reduction in lumen caliber 50% occurs during a provocative test and reversal is achieved with intracoronary nitroglycerin.

Treatment typically consists of medical therapy with calcium channel blockers and/or nitrates. Blockers should be used with caution as patients may experience a worsening of their symptoms due to unopposed alpha stimulation.The long-term prognosis of patients with variant angina is generally good if the patient is treated and avoids certain provocative stimuli.[1]

Microvascular Abnormalities

Patients with chest pain and/or evidence of myocardial ischemia and NOCAD and no other obvious epicardial etiology should undergo evaluation for abnormalities in the coronary microcirculation.With an increase in myocardial oxygen demand,there is an increase in coronary blood flow.The ability to increase coronary blood flow in response to vasoactive stimuli is termed *coronary flow reserve* (CFR). CFR is determined by the ratio of maximal coronary blood flow to the resting coronary blood flow.The major epicardial coronary arteries only contribute about 5% to the total coronary vascular resistance.

The majority of coronary vascular resistance originates in the coronary arterioles, typically less than 300µm. Changes in the microcirculation may result in dramatic alterations in coronary blood flow and CFR, which may provoke ischemia. Cannon and Epstein proposed the term *microvascular angina* in 1985 for the symptoms of angina pectoris and a positive stress test in the setting of no significant epicardial stenosis.In the presence of normal epicardial arteries and normal microvasculature, the CFR is normal. However, severe flow-limiting epicardial stenosis or microvascular pathologic states of the coronary arterioles results in the diminution of CFR. Several pathologic entities are known to affect the coronary microcirculation. All can lead to some abnormality in coronary blood flow through endothelial dependent or independent mechanisms.

Therefore, patients with chest pain and NOCAD should undergo assessment of endothelial dependent and independent abnormalities of the microcirculation,especially in the setting of disease states known to affect the microcirculation.

Endothelial Dysfunction

The endothelium plays a pivotal role in coronary homeostasis. It regulates vascular tone and coronary blood flow by releasing endothelial derived vasodilating factors such as nitric oxide (NO) and

endothelial derived vasoconstrictors such as endothelin. It also plays a role in many physiologic processes such as inflammation,thrombosis, and platelet activation.

Acetylcholine (ACh) stimulates the release of NO from normal endothelium, which then activates guanylate cyclase leading to an increased production of cyclic guanosine monophosphate and a reduction in intracellular calcium. It is apparent that NO is a key factor in vascular physiology and its bioavailability is vital in the maintenance of endothelial health. The degradation of NO is enhanced by reactive oxidant species such as superoxide anion and oxidized low-density lipoprotein (LDL) cholesterol and this reduction in the bioavailability of NO can lead to abnormal coronary physiology.

Both invasive (with intracoronary ACh) and noninvasive (reactive hyperemia using brachial artery ultrasound) assessments of endothelial function have been reported.In coronary arteries with normal endothelium, the response to intracoronary ACh is epicardial and microvascular dilation resulting in an increase in coronary blood flow. However, when the endothelial lining is disrupted, intracoronary ACh induces vasoconstriction and a decrease in coronary blood flow. This endothelial-dependent response to ACh may serve as a marker for the bioavailability of NO. Moreover,the abnormal coronary constriction response to ACh suggests a lack of NO bioavailability and denotes endothelial dysfunction.

The fact that the epicardial arteries may be angiographically free of disease does not preclude endothelial dysfunction; atherosclerosis may not be evident secondary to remodeling, diffuse disease, or may in fact be absent, as endothelial dysfunction is considered an early stage of atherosclerosis.

Moreover, several studies have demonstrated that endothelial dysfunction is not just a risk factor and marker for developing atherosclerosis, but that inducible ischemia has been demonstrated in patients with nonobstructive coronary arteries and abnormal endothelial testing.Abnormal endothelial

function serves as a prognostic indicator to future cardiac events. Treatment for endothelial dysfunction can be challenging and should always include risk factor modification with diet,exercise, tobacco cessation, blood pressure control, glucose control, and lipid management.

Several studies have demonstrated abnormal coronary flow reserve in hypercholesterolemic or diabetic patients with NOCAD.Statins may have a significant benefit in patients with endothelial dysfunction by improving lipid profiles and possibly through other mechanisms such as reduction of inflammation.[1]

C-reactive protein is a marker of systemic inflammation that has been shown to correlate with future cardiac events.It has also been suggested that elevated C-reactive protein is associated with the development of endothelial dysfunction.Blunted endothelial function has been demonstrated in patients with elevated C-reactive protein.

Nonepicardial, Nonmicrovascular causes for Chest Pain

This group is the largest and most diverse of the three groups. It includes all other disease states not related to epicardial or microvascular disease.It is important to realize that these patients may still have a cardiac etiology for their pain, such as pericarditis.They should all be kept in mind when evaluating the etiology of chest pain in a patient with NOCAD. Moreover, if the epicardial and microvascular assessments are normal, than consultation with other specialists is important to help define the etiology of the chest pain.

Pericarditis

Pericardial and/or myocardial inflammation can mimic ischemic chest pain. Typically, the pain is described as sharp, retrosternal, and is aggravated by lying flat and improved by sitting up. The

physical exam may reveal a pericardial friction rub or pericardial knock. The electrocardiogram usually demonstrates diffuse ST-segment elevation. However, the upward concavity of the ST segment, absence of Q-waves and T-wave inversions, help to distinguish pericarditis from acute coronary syndromes. Pericarditis often responds well to nonsteroidal anti-inflammatory agents.

Vascular

Thoracic aortic dissection is the most common catastrophe of the aorta, 2 to 3 times more common than rupture of the abdominal aorta. When left untreated, about 35% of patients die within the first 24 hours, and 50% die within 48 hours. The pathologic features of aortic dissection consist of a tear in the intimal layer, followed by formation and propagation of a subintimal hematoma. If the pericardial space is involved in the dissection, cardiac tamponade may result.

Chest pain is the most common presenting complaint in patients. The pain usually is described as ripping or tearing; however, this description is not universal, and some patients present with only mild pain. Patients may present with ischemic pain and electrocardiographic changes, if the coronary arteries are involved with the dissection.

Smoking and hypertension are the most common risk factors associated with dissection.Although aortic dissection or penetrating aortic ulcers are unlikely to cause intermittent pain over several weeks, they should be considered in all patients complaining of acute, sudden, and severe chest pain that is maximal at onset. Diagnosis is best obtained with computed tomography or transesophageal echocardiography.

Gastrointestinal

Sir William Osler first described the esophagus as a source of episodic chest pain in 1892.

Esophageal abnormalities represent a significant percentage of patients with noncardiac chest pain (15% to 60%) and although gastroesophageal reflux disease and esophageal spasm are the most common causes for chest pain originating from the gastrointestinal tract, one should also consider biliary colic, cholecystitis, and peptic ulcer disease.

It is not inconceivable that esophageal abnormalities produce similar symptoms as cardiac ischemia because the distal esophagus and the heart have a common afferent nerve supply. History is often not helpful in discerning cardiac from esophageal chest pain because both can induce pressure or burning chest discomfort, which is exertional in nature.

Response to nitroglycerin is not a helpful clue either; nitroglycerin can relieve the discomfort produced by esophageal spasm by relaxing smooth muscle or via placebo effect. Also, patients with cardiac and esophageal pain often have similar risk factors, namely, tobacco use and obesity. Endoscopy, manometry, and 24-hour pH monitoring have all been advocated in the work up of patients with chest pain and NOCAD.

However a short course of proton pump inhibition is more sensitive and specific for determining the cause of chest pain than endoscopy, manometry, or 24-hour pH monitoring. It may be reasonable to consider acid suppression therapy in patients prior to an extensive gastrointestinal workup. If the cardiac work-up is unremarkable, all patients with chest pain and NOCAD should be carefully screened for the occurrence of esophageal disorders. Referral to a gastroenterologist may be prudent.

Pulmonary

Several pathologies in the pulmonary system may lead to chest pain and should be considered in patients with chest pain and NOCAD. Important ones to rule out are pneumonia, pneumothorax, and

pulmonary embolism.The first 2 should be readily apparent with history, physical exam, and radiographs; however, Pulmonary Embolism frequently goes undiagnosed and leads to significant morbidity and mortality. It is estimated that pulmonary embolism leads to 50,000 to 200,000 deaths annually in the United States. The most common symptoms reported in pulmonary embolism include dyspnea, chest pain, and cough.

Patients often develop tachypnea, rales, and/or tachycardia. However, chronic pulmonary embolism can lead to less dramatic symptoms and patients may present with pulmonary hypertension.Diagnosis is best obtained with computed tomography or pulmonary angiography. Therapy consists of anticoagulation.

Musculoskeletal

Tietze syndrome is characterized by benign, localized, painful, swelling of an upper costochondral area, without any evidence of overlying disease. The cause is unknown and the syndrome usually occurs in the second through fourth decades of life. Tietze syndrome likely represents a small segment of the chest pain population.

Epstein found that only 10% of patients seen for chest pain had a costochondral syndrome. Although it can be debilitating and associated with significant pain, it is typically self-limiting and patients often obtain relief with nonsteroidal anti-inflammatory drugs.[(1)]

Enhanced Pain Perception/Psychogenic Pain

Psychological factors have been suspected as a cause of non cardiac chest pain for more than a century.It is found that 1 in 4 patients consulting an ambulatory emergency department for chest pain suffer from panic disorder.

Enhanced pain perception has also been demonstrated in patients with chest pain and NOCAD.Intracardiac catheter manipulation produced typical chest pain in 34 of 36 patients with NOCAD, in the absence of any changes in Coronary Blood Flow and that the same stimulus caused chest pain in only a small proportion of patients with coronary artery disease. A lower threshold for pain perception could explain the occurrence of chest pain in these patients without involving an ischemic mechanism.

Treatment and diagnosis of chest pain secondary to enhanced pain perception or psychiatric abnormalities can be difficult and many patients may not accept this explanation. Most patients benefit from counseling, which helps in reducing further health care utilization. Medical therapy often consists

of tricyclic antidepressants such as imipramine or benzodiazepines. Nonpharmacologic therapies may include biotherapy or spinal cord stimulators. Spinal cord stimulation has been shown to reduce symptoms and increase exercise capacity in patients with chest pain and NOCAD.

More recently in patients with chest pain and normal coronary arteries and it was found that elevated C-Reactive Protein levels correlated with symptoms and electrocardiographic markers of myocardial ischemia. A number of studies have demonstrated that C-Reactive Protein levels can be lowered with statin therapy.It is plausible that statins may improve endothelial function by reducing or preventing inflammation.

Other therapies, such as angiotensin converting enzyme inhibition and anti oxidants have also shown some benefit in endothelial dysfunction. We have shown that oral L-arginine (a precursor to NO) improves endothelial function and symptoms at 6 months.It is important to assess secondary conditions associated with chest pain and abnormal CFR, such as, hypertensive heart disease, valve disease, cardiomyopathy.

DIAGNOSIS

When evaluating patients with chest pain, the role of the cardiologist is to determine if symptoms are related to a cardiac etiology. It is important to realize that patients with NOCAD may need further testing after angiography and echocardiography.The assessment of both endothelial-dependent and -independent epicardial and microvascular abnormalities can often lead to a cardiac diagnosis that may have otherwise been missed. This in turn allows appropriate treatment options to be initiated and better outcomes for patients.

Angiographic assessment of epicardial coronary artery blood flow has played a pivotal role in our understanding of the "time-dependent open artery hypothesis" and in the evaluation of reperfusion strategies over the past 2 decades.But it has become increasingly apparent,that clinical outcomes are not only associated with angiographic flow in the epicardial artery, but also with angiographic flow in the myocardium.To this end, the goal of reperfusion therapies has shifted to include reperfusion downstream at the level of capillary bed, and it might be more appropriate that the hypothesis now be termed "the time dependent open artery and open microvascular hypothesis."[52]

Although the TIMI (Thrombolysis In Myocardial Infarction) flow grade classification scheme is widely used to assess angiographic outcomes, it is limited by poor reproducibility and its categoric nature. The corrected TIMI frame count (CTFC) is a simple, more objective continuous variable index of coronary blood flow that can be broadly and inexpensively applied. This measure of the time for dye to traverse a coronary artery is both accurate (highly correlated with Doppler velocity measurements) and precise (reproducible).

The method has been prospectively validated as providing independent risk stratification above and beyond the conventional TIMI flow grades. It has been shown to be a predictor of restenosis, and

has been of value in elucidating the underlying pathophysiology of acute myocardial infarction. In view of the above and its ease of use, it is anticipated that CTFC will become a widely used method to evaluate coronary blood flow.[52]

Some important practical caveats exist. The measurement of CTFC from coronary angiograms is a bit operator-dependent. Important variables exist that significantly affect the CTFC. The dye injection rate and catheter size have no effect on CTFC. However, nitrate use, heart rate, and the phase of the cardiac cycle in which dye is injected have a significant effect on CTFC. Therefore, studies comparing the CTFC need to consider these factors.[53]

Restoration of epicardial flow does not necessarily lead to restoration of tissue level or microvascular perfusion, as elegantly documented by Ito et al on myocardial contrast echocardiography. Perfusion of the myocardium can also be assessed using the angiogram. In the Tissue Myocardial Perfusion Grade System (TMPG), TMPG 0 represents minimal or no myocardial blush; in TMPG 1, dye stains the myocardium, and this stain persists on the next injection; in TMPG 2, dye enters the myocardium but washes out slowly so that dye is strongly persistent at the end of the injection; and in TMPG 3, there is normal entrance and exit of dye in the myocardium.[52]

Another method of assessing myocardial perfusion on the angiogram is the myocardial blush grade (MBG) developed by van't Hof et al.A grade of 0 (no blush) and a grade of 3 (normal blush) are the same in the TMPG and MBG systems. An MBG grade 1 or 2 represents diminished intensity in the myocardium and corresponds to a value of 0.5 in the expanded TMPG grading system. A TMPG of 1 or a stain in the TIMI system is subsumed within the value of a 0 in the MBG system. Thus,normal perfusion in the myocardium carries a score of 3 in both the TMPG and MBG systems, and a closed muscle carries a score of 0 in both systems[52].

There are data associating abnormal myocardial perfusion on the angiogram with slower Doppler velocity measurements in the epicardial artery.Does abnormal myocardial perfusion slow epicardial flow, or, alternatively, does abnormal epicardial flow impair myocardial perfusion? Although there is likely a bidirectional nature to any causal relationship between the two, after restoration of full epicardial patency (eg, after the scaffolding of the lesion by intracoronary stent placement), it is likely that impaired myocardial perfusion may play a major role in reducing antegrade flow in the epicardial artery. A variety of drugs are available to treat abnormal myocardial perfusion, but aside from adenosine, their association with improved clinical outcomes remains largely untested. (52)

There is the need for a simple, broadly applicable angiographic metric that takes into account indices of epicardial and myocardial perfusion to arriveat a single perfusion grade. The Angiographic Perfusion Score (APS) is the sum of the TFG (0 to 3) added to the TMPG (0 to 3) before and after PCI (total possible grade of 0 to 12).Failed perfusion can be defined as an APS of 0 to 3; partial perfusion, 4 to 9; and full perfusion, 10 to 12.(52)

PROGNOSIS

Overall, once life threatening diseases are excluded (Aortic Dissection, Pulmonary Embolism etc.), patients with chest pain and NOCAD have an excellent long-term prognosis despite continued symptoms.In a large number of patients with chest pain and normal coronary angiograms,the survival after a 7-year follow-up was 96%.(1)About one third of the deaths, however, were cardiovascular in origin. As noted, several studies have shown that patients with endothelial dysfunction are at risk for subsequent cardiac events and it is this subpopulation that may contribute to the cardiac mortality seen in patients with chest pain and NOCAD.

CHEST PAIN CLINIC

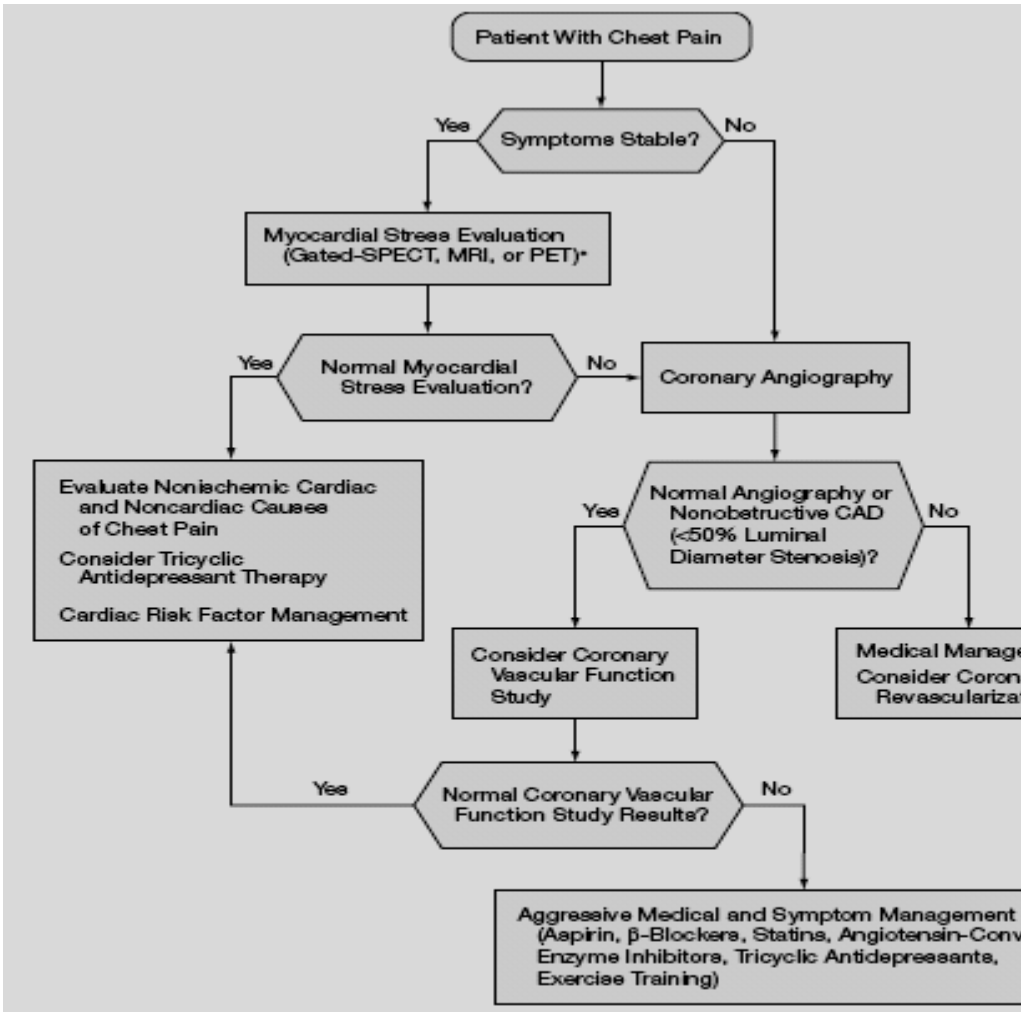
The difficulty and extensive resource utilization in diagnosing and treating patients with NOCAD has led many institutions to develop a specialized chest pain clinic, which utilizes a multidisciplinary approach to patient care. This allows thorough investigation, patient education, and frequent follow-up. Patients undergo lifestyle modification counseling and meet with dieticians and tobacco cessation specialists as needed. Patients with NOCAD and chest pain often have ongoing symptoms and may require frequent follow- up to avoid further hospitalizations and unnecessary evaluations. This can be accomplished with the utilization of a chest pain clinic.

In today's era of the informed patient, reassurance is usually not adequate and patients will want an explanation as to why they have chest pain. Without a sincere attempt to make a diagnosis, most patients remain frustrated and return to seek medical care.Educational opportunities, multidisciplinary personnel, and regular follow-up are key benefits of a chest pain clinic that may reduce health care utilization and improve patient satisfaction

SUMMING UP

The diagnosis and treatment of patients with NOCAD can be a complex and time consuming responsibility. A logical classification and step-wise approach is needed to avoid significant expense and unnecessary testing. The prognosis for these patients, with few excepted diagnoses, is quite good and reassurance, education, and follow-up are important in their management (Figure 1).

Practical Algorithm for Management of Patients With NOCAD



MRI indicates magnetic resonance imaging; PET, positron emission tomography; CAD, coronary a
ease. Vascular function studies include coronary flow reserve and coronary acetylcholine testing. Al
should have cardiac risk factor management, as appropriate, according to the American Heart Ass
American College of Cardiology guidelines.[76,77]
*Which specific test to obtain depends on patient and institutional circumstances. In some cases se
may be needed (eg, first a stress electrocardiogram or echocardiogram followed by gated single-phot
sion computed tomography [SPECT]).

Figure 1

LITERATURE REVIEW

Literature search was conducted with the help of the Internet scientific search engine Scirus @ www.scirus.com (Elsevier Inc) from their start dates until December 2006 for study using specific key words "Coronary Slow Flow Phenomenon","Non Obstructive Coronary Artery Disease" and "Corrected TIMI frame count".The relevant literature was sourced from online as well as print versions.

The literature was classified for study purpose depending on the source and relevance to study in to 1) Relevant standard text-book chapters,2)Periodical material which was sub-divided in to a)Review articles on CSFP, b)Review articles on CTFC methodology,c)Original papers on various niche problems associated with CSFP,finally d) Review article on approach to patient with NOCAD, and 3) Relevant full text clinical practice guidelines published by a contemporary leading professional society.

Cardiologists are familiar with the phenomenon of slow progression of angiographic contrast in the coronary arteries in the absence of stenosis in the epicardial vessels in some patients presenting with chest pain.

The coronary slow flow phenomenon (CSFP), first described in 1972 by Tambe et al.remains scantily studied.[3,9]This phenomenon should be distinguished from occurrence of slow flow in the context of coronary reperfusion therapy such as angioplasty or thrombolysis that is associated with different pathophysiological and clinical implications. Similarly, coronary slow flow associated with coronary artery spasm, coronary artery ectasia, myocardial dysfunction, valvular heart disease and certain connective tissue disorders involving coronary microvasculature is easy to understand.[4,10]CSFP may occasionally also result from inadvertent air-embolism during angiography or may be due to an

overlooked ostial lesion.

However, it is not certain whether CSFP in the absence of any of these known causes represents merely an angiographic curiosity or has special physiologic or therapeutic implications.

Overall, CSFP is observed in approximately 1% of the patients undergoing CAG, especially in patients presenting with acute coronary syndrome. In the Thrombolysis In Myocardial Infarction (TIMI)-IIIA study, 4% of patients presenting as unstable angina but with normal / insignificant epicardial coronary artery disease (CAD) showed impaired angiographic filling suggestive of CSFP.[5] Mangieri et al.[6]reported an incidence of 7% of this phenomenon in patients suspected to have CAD, however the documentation of slow flow was visual without any objective criteria.

Usually TIMI flow grade scheme is followed to assess coronary blood flow. It reflects the speed and completeness of the passage of the injected contrast through the coronary artery.[7,8]This method is a qualitative way of assessing coronary flow and is limited by significant inter-observer variability. In contrast, corrected TIMI frame count (CTFC) is a more quantitative and reproducible index of coronary artery flow.[51,52]It represents the number of cine frames required for contrast to reach the standardized distal coronary artery landmarks. CSFP is defined as CTFC greater than 2 standard deviations (SD) from normal published range for that particular vessel.[51,52]

CSFP is more often seen in males who are current smokers.[11]This is in contrast to “Cardiac syndrome X” which is predominantly a disorder of post-menopausal females.[11]Patients with CSFP more often present with rest pains, requiring urgent hospital admission. Both resting electrocardiographic (ECG) abnormalities as well as positive Treadmill Test (TMT) are more frequent in patients with slow flow as compared with patients having normal coronary flow.

Myocardial perfusion scintigraphy shows reversible perfusion abnormalities in 30-75% of such

patients.[12,13]On long-term follow-up the clinical course is usually benign in patients with CSFP, although it is frequently punctuated with remitting, relapsing anginal episodes resulting in considerable impairment in quality of life.[14]Over 80% of these patients experience recurrent chest pain and one third of them require readmission for an acute exacerbation.[15]Occasionally, patients may present with evidence of acute myocardial infarction.[16]

Recently, Atak et al.[17]have reported abnormalities of corrected QTdispersion in patients with CSFP. Whether this predisposes to ventricular arrhythmias and sudden cardiac death in these patients is not clear.

The pathophysiological mechanisms of CSFP remain uncertain. Several hypotheses however, have been suggested for slow coronary flow phenomenon, including a form of early phase of atherosclerosis, small vessel dysfunction, Hagen–Poiseuille's equation model, imbalance between vasoconstrictor and vasodilatory factors, and platelet function disorder. More recently, there has been mounting evidence that inflammation plays an important role in the initiation, development as well as evolution of atherosclerosis, suggesting that atherosclerosis is an inflammatory disease. New evidence has also indicated that inflammation may be involved in the development of slow coronary flow phenomenon.[2]

The coronary circulation is traditionally considered as a two-tier model. The first tier consists of epicardial vessels, which are also referred to as "conductance vessels" as these do not pose any resistance to blood flow. The second tier consists of "small vessels" of <400 μm ("resistive vessels") which primarily regulate myocardial blood flow in the absence of any significant obstructive epicardial stenosis.[18]

"Small vessel dysfunction" has been typically implicated in the pathogenesis of CSFP since its

first description.The evidence of affliction of small vessels comes from the results of histopathological examination of ventricular biopsy specimens in patients with CSFP.[6,19]Mosseri et al.[19] reported abnormalities of small coronary arteries along with myocardial hypertrophy and patchy fibrosis in the biopsy samples from right ventricle of six patients with CSFP. However, majority of these patients had concomitant diseases that could have induced these changes.

Later, Mangieri et al.[6]reported histopathological examination of left ventricular endomyocardial biopsy specimens in a more homogenous group of 10 patients of CSFP who did not have any other cardiac or systemic diseases. There was evidence of small vessel affliction i.e. endothelial thickening due to cell edema, capillary damage and reduced luminal diameter of the small vessels.

Electron microscopy revealed irregular nuclear morphology and several indentations of the nucleolemma and pyknosis. But it is not certain whether slow flow

leads to these histopathological changes or whether these changes cause slow flow, though the later appears more likely.[12]Also, these fixed structural changes cannot explain the acute presentation in the majority of these patients.

The clinical and angiographic variability implies a significant dynamic component to the coronary microvascular resistance. It is noteworthy that only a third of the patients with CSFP fulfilled the criteria on a repeat angiographic study.[15]Thus CSFP lacks reproducibility.It is postulated that this dynamic increase in microvascular tone is due to “microvascular spasm” resulting in recurrence of symptoms. Exact mechanism for this dynamic response is not well elucidated. It is plausible that intermittent release of certain autacoids (neuropeptide-Y, endothelin-1, thromboxane-A2 etc.) mediate

coronary vasoconstriction.[15,20-22]

Even invasive hemodynamic and metabolic parameters do not consistently suggest a uniform mechanism for CSFP. Resting hemodynamic parameters of heart rate, blood pressure or the double product fail to explain the occurrence of CSFP.[13,15]The vasodilatory response of the microvasculature to provocative stimuli is less clear and has evoked mixed responses.[15,23]Lower resting coronary sinus oxygen saturation has been observed in patients with CSFP as compared to controls for a similar myocardial oxygen demand.[15]This implies a higher transcoronary myocardial extraction caused by the delayed resting coronary perfusion consistent with CSFP. Whether this delayed perfusion results in myocardial ischemia either during rest or during stress needs to be addressed.

Yaymaci et al.[24]investigated the presence of stress-induced myocardial ischemia in patients with CSFP by measuring two metabolic indicators of ischemia i.e. coronary arteriovenous oxygen content difference and lactate production. Although majority of patients developed anginal pain with atrial pacing, only few (17%) revealed evidence of metabolic ischemia. Thus, angina pectoris in most patients with CSFP does not originate from myocardial ischemia as demonstrated by metabolic parameters. However, of the subset of patients who showed evidence of metabolic ischemia, majority showed a perfusion defect using single photon emission computed tomography (SPECT) that anatomically correlated well with the vessel showing CSFP. These differences in patients with CSFP may be explained by the variability in the degree of coronary flow reserve (CFR), which, per say, is an indicator of microvascular function.

Recently, Sezgin et al.[25]reported evidence of endothelial dysfunction in patients with CSFP using simple method of measuring flow-mediated vasodilation of the brachial artery. It has been suggested that flow-mediated vasodilation is predominantly due to endothelial release of nitric oxide.There was a strong and inverse relationship between CTFC and percentage of flow-mediated

vasodilation in patients with CSFP thereby suggesting that endothelial nitric oxide activity is impaired in these patients.[25]

It is well appreciated that diffuse atherosclerosis may be present in angiographically normal appearing vessel. Further, macro- and microvascular disease may also coexist.[26,27]A recent study investigated the significance of epicardial vessel affliction by studying coronary anatomy using intravascular ultrasound (IVUS) and measuringepicardial resistance using fractional flow reserve (FFR) in patients with CSFP.[27]FFR is an index of resistance to flow along the epicardial vessel and is defined as the ratio of distal to proximal coronary pressures.[18]In maximal hyperemia (e.g. adenosine-induced), FFR is independent from microvascular bed. If there is no resistance along the artery as expected in normal epicardial artery, there is no pressure decline and FFR approaches unity. Surprisingly, a decline in the distal coronary pressure leading to significantly lower FFR value was seen in the patients exhibiting slow flow phenomenon.

There was a strong negative correlation between CTFC and FFR. Interestingly, the patients showing perfusion defects using myocardial perfusion scintigraphy had significantly lower FFR values, signifying even higher epicardial resistance. There was diffuse intimal thickening and calcification throughout the epicardial arteries on IVUS. A negative correlation was observed between intimal thickness and FFR. It is postulated that decreased FFR levels are due to increased resistance in the epicardial coronary arteries resulting from diffuse atherosclerotic disease as demonstrated by IVUS.[27]

Thus, at present, the data are not sufficient to delineate the borders of this phenomenon. Whether it is due to involvement of predominantly macro- or microvasculature of the heart is not certain. It is hypothesized that CSFP may be a form of early phase of atherosclerosis in some patients.However, certain other factors may also contribute to CSFP.

It appears that CSFP may represent a heterogeneous group of disorders unified because of characteristic angiographic appearance. Slow flow has been characteristically seen in ectatic and aneurysmally dilated coronary arteries (dilated

coronaropathy) with proportionately more impairment of blood flow in these vessels with increasing coronary artery diameters.[28]This is in accordance with the Hagen-Poiseuille's equation which states that resistance to flow within a tube depends on the dimensions of the tube and the viscosity of the fluid in it.[29]

However, the relationship of CSFP in relation to vessel diameter has not been well studied. Furthermore,importance of other rheological factors, blood viscosity, fibrinogen levels and hyperlipidemia (contributing to increased blood viscosity) in these patients has not been studied. Hematocrit and fibrinogen are the major determinants of blood viscosity. Increased blood viscosity leading to decrease in coronary blood flow reserve has been associated with hyperlipidemia and high fibrinogen levels.[29,30]The therapeutic implications, if any, of these findings remain to be studied.

Other rare causes may be important in appropriate settings. For example, slow coronary filling has been reported in patients with cocaine use even in the absence of coronary artery spasm.[31]

Endothelin-1and Nitric oxide are important molecules that modulate vasodilatory response to stress (rapid atrial pacing/exercise). Recently published studies have highlighted the imbalance between Endothelin-1 and Nitric oxide release in patients with CSFP as compared to controls with normal coronary flow.[32,33]No significant difference in arterial and coronary sinus Nitric oxide plasma levels was seen in the two groups, at baseline as well as after pacing. In contrast, basal plasma Endothelin-1 levels were higher in patients with CSFP. Rapid atrial pacing resulted in significantly higher coronary sinus levels of Endothelin-1 in patients with CSFP, which also correlated well with the CTFC.

Furthermore, in patients with CSFP, coronary sinus Endothelin-1 levels also increased significantly as compared to femoral artery Endothelin-1 levels. Even correlation of Endothelin-1 levels and intimal thickness of coronary artery using IVUS has been reported.[32]It is possible that CSFP results from imbalance of Endothelin-1, a potent vasoconstrictor leading to deregulation of vascular tone even in the very early stages of plaque formation. More studies are required to unravel the molecular mechanisms of CSFP.

There are no definite treatment modalities for patients with CSFP. Conventional antianginal therapy is of limited value in the chronic management in these patients.[34]Nitrates are ineffective as their biotransformation to active metabolite is diminished due to deficiency of required enzymes in coronary microvessels as compared to larger epicardial coronary arteries.[35,36]

In contrast, dipyridamole may be effective due to its predominant action on the small vessels of diameter less than 200 μm. It blocks uptake of adenosine by both vascular endothelium and erythrocytes and prevents its conversion to inactive metabolites. This results in re-distribution of vascular resistances due to vasodilation of the small vessels.[36,37]

Mangieri et al.[6]demonstrated the effectiveness of dipyridamole in acute setting during coronary angiography in patients with CSFP.

Intracoronary administration of this drug relieved microvascular tone and accelerated contrast run-off in coronary arteries without changing the diameter of epicardial coronary vessels. As expected, intracoronary nitroglycerine failed to produce any beneficial effect in these patients. Demirkol et al. [12]also observed improvement in myocardial perfusion with dipyridamole infusion using myocardial perfusion Single Photon Emission Computed Tomography.

Long-term oral therapy with dipyridamole was assessed by Kurtoglu and associates[38] in an

open-label fashion. Coronary flow returned to normal levels in majority of the vessels as adjudged by using CTFC. This was accompanied with complete relief from chest pain in two-third of patients and decrease in symptoms in the remaining. Since this phenomenon, per say, is punctuated by remissions in clinical course, more data using case control studies are required to confirm the above observations.

Conventional calcium L-channel blockers (diltiazem/ verapamil) are of limited value in alleviating symptoms. This is perhaps due to absence of voltage-gated L-type calcium channels in microvessels, as shown by studies in the animalmodels.[39]Instead, the microvascular tone may appear to rely on other types of voltage-gated calcium channels, possibly of the T-type.[40]Mibefradil is a long-acting calcium T-channel antagonist that was approved by FDA in 1997 for the treatment of hypertension and chronic stable angina pectoris. Unfortunately the drug was voluntarily withdrawn shortly after its launch due to its numerous clinically relevant drug interactions.[41]

Recently, Beltrame et al.[34]assessed the acute and long-term clinical benefits of mibefradil in patients with CSFP by exploring its beneficial effects on microvessels. There was significant acute angiographic improvement in coronary flow indices with this drug. CSFP was abolished in approximately three fourth of the vessels at 30 min after the drug intake. This occurred without any significant changes in the epicardial vessel diameter or rate-pressure product.

Interestingly, the improvement in flow indices occurred primarily in vessels with CSFP as compared to vessels with normal epicardial flow. In accordance with these acute angiographic results, long-term clinical benefits with this drug were also observed. In a randomized, double blind, placebo controlled, cross-over study, there was substantial reduction in frequency of angina by 56% ($p<0.001$), episodes of prolonged angina by 74% ($p<0.001$), and sublingual nitrate consumption by 59% ($p<0.01$) along with improvement in physical quality of life ($p=0.003$).[34]Since the drug has been formally withdrawn, these observations may stimulate further research with similar molecules.

Recently, a three-dimensional pharmacophore model consisting of three hydrophobic regions,

one hydrogen bond acceptor and one positive ionizable region has been hypothesized for T-type calcium channel blockers.[42] Whether it acts as a valuable tool in designing new ligands for this group of drugs remains to be seen.

Thus,CSFP continues to intrigue the clinicians. It appears to represent a heterogeneous group of disorders. In some it may represent an early stage of atherosclerosis with endothelial dysfunction and in others it may indicate microvascular dysfunction or other unknown disorders. The prognosis appears good although symptoms tend to recur. Further advances in the understanding of pathophysiologic mechanisms and treatment of CSFP are awaited.

AIM & OBJECTIVE

AIM

This study addresses a major problem of contemporary cardiology.In the cardiovascular out-patient department,we commonly see patients presenting with angina pectoris,during the disease attack angiographically normal coronary arteries were eventually demonstrated. These patients are usually characterized by the following clinical features: usually young,angina pectoris for a long duration without other accompanying cardiovascular disease but significant slow coronary distal flow in one or multiple vessels.

The mechanism for this clinical setting of coronary artery disease is unclear,but the patients have commonly large epicardial coronary arteries, which may suggest a hemodynamic mechanism of coronary disorder.Evincing a keen interest in the phenomenon,it was investigated further and hence this study.

Only a limited number of studies have focused on the etiology of this unique angiographic phenomenon.Four clinical types of Coronary Artery Disease (CAD) have been classically defined, that is,chronic stable angina pectoris (CSA),variant angina pectoris,silent angina pectoris and cardiac syndrome X.

However patients presenting with coronary slow flow phenomenon in NOCAD are hard to be classified into one of these.Whether this is really a new kind of coronary disease is still unknown and deserves further investigation.It is suggested that these patients may be reclassified into a new clinical entity called as ‘‘Coronary Slow Flow Syndrome’’.

OBJECTIVE

It has been an interesting journey from “Coronary Slow Flow - An angiographic curiosity” through “Coronary Slow Flow Phenomenon – A recognized angiographic entity in Non Obstructive Coronary Artery Disease” to “Coronary Slow Flow Syndrome - A novel Non Obstructive Coronary Artery Disease ?” In this study it is hypothesized that “Coronary slow flow syndrome” is a novel subset of Non Obstructive Coronary Artery Disease with distinct features.To prove the hypothesis it is aimed to study the Coronary Artery Disease characteristics peculiar to ‘‘Coronary Slow Flow Phenomenon” in a population of patients with Non Obstructive Coronary Artery Disease.It is intended to achieve the aim through a set of objectives which permit a comparison of disease characteristics of the slow flow group with that of a control group having normal flow.

The objective of the study may be crystallized in to the following :

1. Compare and analyze the demographic characteristics,clinical features,Coronary Artery Disease risk factor profile,anti anginal medication profile of coronary slow flow versus normal flow in patients with Non Obstructive Coronary Artery Disease,

2. Compare and contrast total work load,total exercise duration and ECG parameters of maximum ST depression,time to onset of ST depression,time to offset of ST depression on Tread Mill Test of coronary slow flow versus normal flow in patients with Non Obstructive Coronary Artery Disease,

3. Follow up patients with coronary slow flow and normal flow in a Non Obstructive Coronary Artery Disease population for detection of “anginal episode” and “hospitalization for angina” as the end point.

METHODOLOGY

1. Setting

The setting is the Cardiology Department of a tertiary level teaching hospital in a metropolitan city.

2. Study design

This is an descriptive and an observational,case-controlled comparative cum prospective cohort study.[55]

3. Study period

This study was carried over a period of two years from January 2005 to December 2006.

4. Study population

The study population was composed of patients with CAD.CAD was defined as patients with known stable chronic CAD on anti-anginal therapy,attending the out-patient clinic of the Cardiology Department.

5. Inclusion criteria

The inclusion criteria was consecutive patients in the study population during the time-period January 1st 2005 to December 31st 2006,who underwent TMT and subsequent Coronary angiography at our department and were found to have NOCAD.NOCAD was defined for study purposes as CAD patients with absolutely normal epicardial coronary arteries without any obstructive or non-obstructive lesion on routine conventional coronary angiography.TMT and Coronary angiography was

performed because subjects enrolled in the study had CAD which could not be adequately clarified on the basis of physical diagnosis alone. [43,44] ACC/AHA practice guidelines were adhered to in evaluating the CAD patients with TMT and Coronary angiography.[43]

There are two groups in this study : A group having NOCAD and slow flow (Group I) and a control group of NOCAD with normal flow.(Group II).

6. Exclusion criteria

Patients in the study population with recent / past acute coronary syndrome,valvular heart disease,pericardial disease,prosthetic heart valve, infective endocarditis, mitral valve prolapse, hypertrophic, restrictive and dilated cardiomyopathy, left ventricular hypertrophy,right ventricular hypertrophy, heart failure,major supraventricular and ventricular cardiac arrhythmia,connective tissue disease,pulmonary, renal,hepatic and hematological disorder,resting ECG changes and ECHO abnormalities were excluded from the study.[44]

7. Study end points

The end point of the prospective-cohort component is “anginal episode” on follow-up which in this study is prospectively defined as 1) Substernal chest discomfort with a characteristic quality and duration that is 2) provoked by exertion or emotional stress and 3) relieved by rest or nitrates.[43]

The end point of the case-controlled comparative component is the clinical and TMT profile namely demographic distribution,coronary risk profile,anti-anginal medication profile,total exercise duration,maximum work load,maximum ST segment depression,time to onset of ST segment depression and duration of ST segment depression in to recovery.

Angiographic end point as a stand alone descriptive component constitutes the characterization

of CSFP in a typical South Asian population.

8. Clinical Assessment

Extracardiac causes of chest pain such as musculoskeletal and gastrointestinal disorders were eliminated in all the patients. Case records were reviewed for detailed history, physical examination, relevant biochemical tests,resting ECG and transthoracic echocardiography (ECHO) data.Atherosclerotic risk factor profile,current anti-anginal therapy-nitrates,beta blockers and calcium channel blockers,patient's body mass index (BMI), blood pressure (BP) , and pulse rate (PR) were also recorded.Angina pectoris was graded according to the Canadian Cardiovascular Society (CCS) grading.All other data was acquired as per contemporary diagnostic criteria.The data was duly entered in a proforma specially designed for study purpose.

9.Follow-up

At follow-up,30 days after the date of coronary angiography all subjects were specifically enquired for the occurrence and frequency of anginal attacks and hospitalization for the same if any.

10.TMT

Each included subject underwent a standard TMT according to the Bruce protocol using Esaote Formula system (Esaote SpA,Italy).ECG Criteria for positivity were horizontal or downsloping ST-segment depression of ≥1 millimetres(mm.) at 80 milliseconds after the J point during exercise or recovery in two or more contiguous leads for study purpose.Total exercise time in seconds(s), Total workload in metabolic equivalents (METS),Time to onset of

ST-segment depression in seconds(s),Magnitude of ST-segment depression in millimeters(mm) and Time to offset of ST-segment depression in seconds (s) were noted.[45]

11. CAG and documentation of CTFC

Subjects underwent selective coronary angiography via the femoral route using standard Judkins technique.[46-50] Coronary arteries were visualized in left and right oblique planes, and cranial and caudal angles using Philips Integris HM 3000 model cine angiography system (Philips Medical Systems Nederland BV, Eindhoven, Netherland).Injection of contrast medium,Urograffin (Ultravist-370; Schering AG, Berlin, Germany) was carried out by hand injection, at a speed of 3–4 mL/s for left coronary artery and 2–3 mL/s for right.Coronary arteriography was recorded at a speed of 12.5 frames per second (fps).CTFC was measured with a frame counter using HCP DICOM Net MFC Application version 4.0 40.0 (SoftLink International Pvt.Ltd).

12. CTFC Methodology

For nearly 2 decades now, the Thrombolysis In Myocardial Infarction (TIMI) flow grade classification scheme (TFG) has been successfully used to assess coronaryblood flow in acute coronary syndromes. It has been a valuable tool to compare angiographic outcomes following reperfusion, and the association of the TFG with clinical outcome (including mortality) has been well documented.The relationship between flow grade and mortality does satisfy what some consider to be 3 criteria required to validate a surrogate end point for mortality, as follows: (1) There is an association between TIMI grade 3 flow and mortality, (2) an agent such as recombinant tissue plasminogen activator improves TIMI grade 3 flow by 22% over another agent such as streptokinase, and (3) the agent tissue

plasminogen activator improves mortality 1.1% over streptokinase.[51-52]

Although the TFG classification scheme has been a valuable tool for comparing the efficacy of reperfusion strategies and in the identification of patients at higher risk for adverse outcomes in acute coronary syndrome, there are limitations to this classification scheme.To overcome these limitations,a new, more objective and precise index of coronary blood flow called the corrected TIMI frame count (CTFC) was developed, in which the number of cine frames required for dye to reach standardized distal landmarks are counted; this is essentially a measure of the time for dye to go down the artery.

Coronary flow was quantified objectively by two independent observers, who were blinded to the clinical details of the individual participants, using the CTFC method as described by Gibson et al.[51]In our center, cinefilming is performed at 12.5 fps. Therefore, a correction has to be made for this difference by multiplying the CTFC observed in these films by a factor of 30 divided by the actual number of frames filmed per second. After assessement of coronary flow in the coronary arteries using the CTFC method, for each group the mean CTFC,which is the mean value of the frame count in the LAD, LCX, and RCA, was obtained from the two groups. Coronary angiograms were analyzed by two blinded observers and their joint opinion was used as an inclusion criteria.

The first frame was defined by a column of contrast extending across >70% of the arterial lumen in anterograde motion. In the first frame used for TIMI frame counting, a column of dye touches both borders of the coronary artery and moves forward.In the last frame, dye begins to enter (but does not necessarily fill) a standard distal landmark in the artery,(Figures 2-3).These standard distal landmarks are as follows: in the RCA, the first branch of the posterolateral artery(PLV); in the circumflex system, the most distal branch of the obtuse marginal branch(OM) and in the LAD, the distal bifurcation, which is also known as the “moustache,” “pitchfork” or “whale’s tail”.

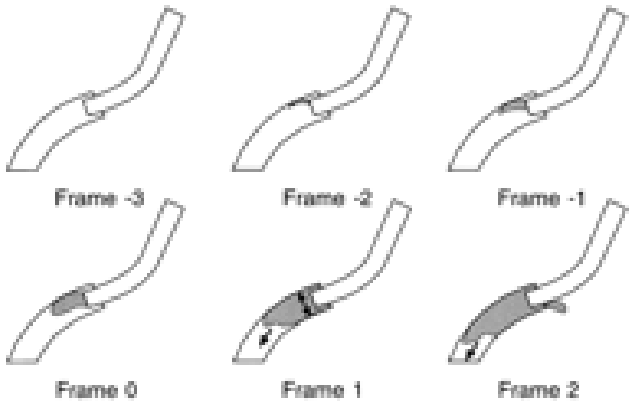


Figure 2 Definitions of the first and last frames used for TIMI frame counting. The first frame used for TIMI frame counting is the first frame in which dye fully enters the artery. This occurs when three criteria are met: (1) A column of nearly full or fully concentrated dye must extend across the entire width of the origin of the artery; (2) Dye must touch both borders of the origin of the artery; and (3) There must be antegrade motion to the dye. Dye may initially track down a single wall of the artery as it leaks from the catheter before the injection, and these frames are not l in the TIMI frame count. If the LAD is subselectively engaged and the LCX is the culprit vessel, the TIMI frame egins when dye first touches both borders at the origin of the LCX. The same rule holds for subselective engagem ıe circumflex artery. The last frame counted is the one in which dye first enters the end-point branch off the targ Note that complete opacification of the target artery is not required, just initial entry of dye into the culprit artery he last frame is best determined by running the cinefilm past the initial opacification of the end-point branch and th g frame-by-frame in reverse until the end-point branch disappears. Care must be taken to advance one more f :ward once the dye disappears to identify the frame in which dye first appears.

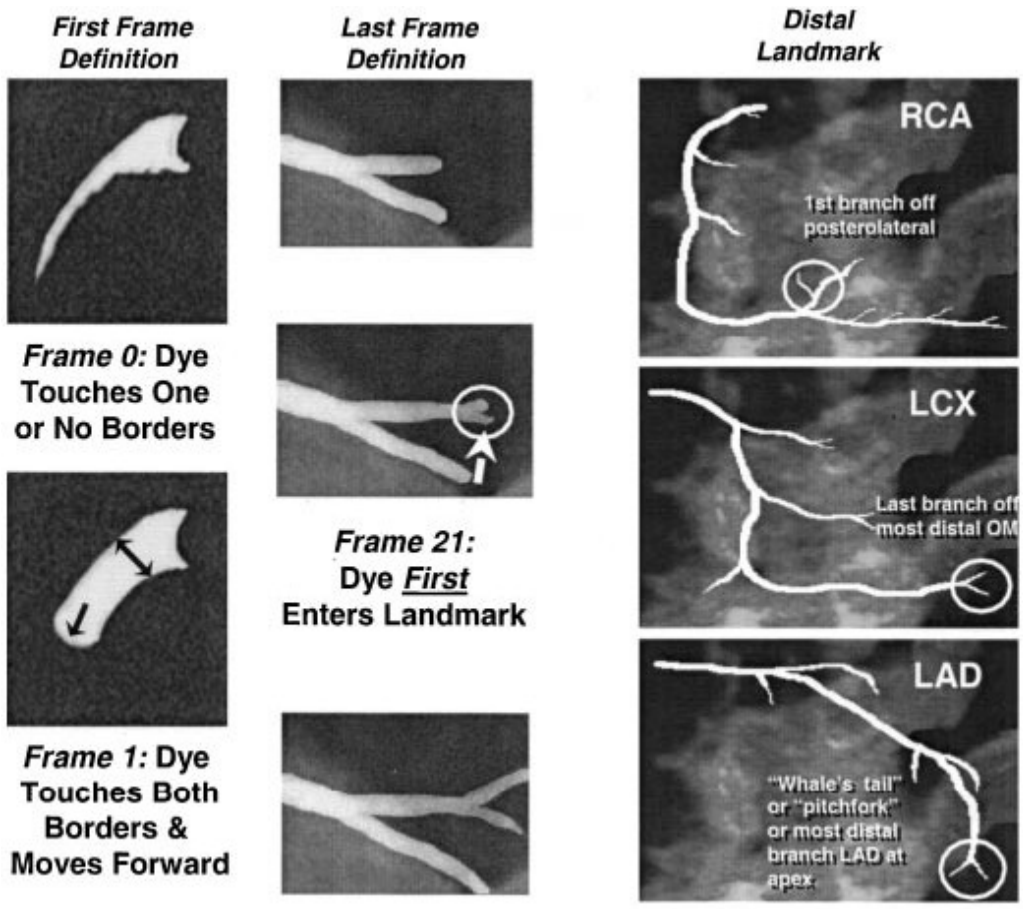


Figure 3 TIMI frame-counting method.In the first frame (lower left panel), a column of near or fully concentrated dye touches both borders of the coronary artery and moves forward. In the last frame (second column), dye begins to enter (but does not necessarily fill) a standard distal landmark in the artery.These standard distal landmarks are as follows: the first branch of the posterolateral artery in the RCA (third column,top panel); in the circumflex system, the most distal branch of the obtuse marginal branch that includes the culprit lesion in the dye path (third column ,middle panel); and in the LAD the distal bifurcation, which is also known as the moustache, pitchfork, or whale's tail (third column, bottom panel).

The normal frame counts for the left anterior descending (LAD) coronary artery are 1.7 times greater than the mean for the left circumflex (LCX) coronary artery and the right coronary artery (RCA). Hence, the longer LAD frame counts were corrected by dividing by 1.7 to derive the CTFC. The CTFC of LAD was assessed in either the right anterior oblique view with caudal angulation or the left anterior oblique view with cranial angulation and that of LCX and RCA in straight left

anterior oblique views.

In multiple studies, the CTFC has been shown to be quite reproducible with a 1- to 2-frame difference between observers.The CTFC is also accurate in that it is highly correlated with Doppler velocity wire measure of CFR, distal velocity, average peak velocity, and volumetric flow,as well as FFR.Normally 21 frames are required for dye to traverse the human coronary artery.Despite differences in the length of the coronary arteries, the force of injections, the diameter of the arteries, heart rates, cardiac output, and catheter engagement, there is only a 3.1-frame standard deviation among patients with normal flow, and the 95% confidence interval for normal flow extends from >14 frames to < 28 frames.

In contrast to the conventional TIMI flow grade system, the CTFC is quantitative rather than qualitative, is a continuous rather than a categorical variable, and is objective, reproducible, and sensitive to flow changes.This simple index of coronary flow allows calibration or standardization of flow grading and should facilitate comparisons of flow data between angiographic trials.[51-54]

13. Definition of normal coronary flow and slow coronary flow

All participants with a CTFC greater than two SD from the normal published range for the particular vessel were accepted as having slow flow while those who have CTFC that fell within the SD of the published normal range for a population of patients with NOCAD were considered to have normal coronary flow. The cutoff values for NOCAD were, defined according to TIMI frame count method by Gibson et al.: 36.2 ± 2.6 frames for left anterior descending, 22.2 ± 4.1 frames for circumflex and 20.4 ± 3.0 frames for right coronary artery. The corrected cutoff value for LAD was 21.3 ± 1.5 frames.[51]

14. Statistical analysis

Statistical analyses were performed with SPSS version 14.0 for Windows(Chicago IL).All continuous variables were normally distributed are expressed as arithmetic mean ± SD and categorical variables as percentage. The acquired data was summarized in to relevant tables and graphs.

2-tailed students t test was used to compare the group arithmetic means of the normally distributed continuous variables and for categorical data, Chi-Square test was used.The null hypothesis was rejected at the 95% confidence interval,considering a probability value of $p < 0.05$ as statistically significant.[55]

RESULT

During the study period 1957 coronary angiograms were performed in our Cardiovascular catheterization laboratory.107 consecutive NOCAD patients in this period constituted the study subjects.

57 patients with angiographically documented CSFP at least in 1 major epicardial coronary artery and otherwise normal coronary arteries formed the study group.These patients were compared with an angiographic control group consisting of the remaining 50 patients found to have absolutely normal coronary arteries with normal coronary flow.

1. Clinical characteristics of study population :

In group I there were 42 males (73%) and 15 females (37%).Group II on the other hand had 22 males (44%) and 28 females (56%).The mean age of slow flow subjects was 54.8 ± 13.8 and that of normal flow 55.7 ± 14.9.The mean BMI was 28.6 ± 4.2 in the slow flow group and 27.9 ± 3.9 in the normal flow,(Table 1).The difference in sex distribution between the two groups was statistically significant.

Table 1

CLINICAL VARIABLE	GROUP-I SLOW FLOW	GROUP-II NORMAL FLOW	P VALUE
AGE	54.8 ± 13.8	55.7 ± 14.9	0.63
MALE / FEMALE	42 / 15(73 / 27) %	22 / 28(44/56) %	< 0.01
BODY MASS INDEX	28.6 ± 4.2	27.9 ± 3.9	0.53

Age in years,Body Mass Index in kg/m^2

2. Hemodynamic characteristics of study population :

Baseline blood pressure – systolic and diastolic and pulse rate is depicted in Table 2.The mean PR in slow flow group was 67.2 ± 7.2 and 71.3 ± 8.2 in the control group.The mean BP was 132.6 ± 8.4 and 84.2 ± 9.6 in slow flow group,128.7 ± 9.7 systolic and 82.4 ± 8.5 diastolic in the normal flow group,(Table 2).The difference in the baseline hemodynamic state between the two groups was statistically insignificant.

Table 2

HEMODYNAMIC VARIABLE	GROUP-I SLOW FLOW	GROUP-II NORMAL FLOW	P VALUE
PULSE RATE	**67.2 ± 7.2**	**71.3 ± 8.2**	**0.46**
SYSTOLIC BP	**132.6 ± 8.4**	**128.7 ± 9.7**	**0.65**
DIASTOLIC BP	**84.2 ± 9.6**	**82.4 ± 8.5**	**0.45**

Pulse Rate in beats per minute,Blood Pressure in mmHg

3. Risk factor profile of study population :

78 % of slow flow group patients were hypertensive versus only 56 % of the control group.The prevalence of diabetes mellitus in the two groups was 68% and 70 % for the slow flow and control groups respectively.64 % of slow group were dyslipidaemic versus 62 % of the normal flow group.An overwhelming 73 % of the slow flow population were active smokers while only 52 % of the normal flow actively smoked.Family history of CAD was elicited in 60 % of the slow flow patients while only 44 % of the normal flow group had a family history of CAD.(Table 3).The

difference in the proportion of patients with risk factors for CAD between the two groups was statistically significant for hypertension,smoking and family history.

Table 3

RISK FACTOR VARIABLE	GROUP-I SLOW FLOW	GROUP-II NORMAL FLOW	P VALUE
HYPERTENSION	44 (78%)	28 (56%)	<0.01
DIABETES MELLITUS	38 (68%)	34 (70%)	0.42
DYSLIPIDEMIA	36 (64%)	31 (62%)	0.63
SMOKING	41 (73%)	22 (44%)	<0.01
FAMILY HISTORY	34 (60%)	22 (44%)	<0.01

Number (%) of patients with the CAD risk factors

4. Anti-anginal medication profile of study population :

Review of current patient prescription for anti anginal therapy revealed that 100 % of patients with both slow flow and normal flow received at least one class of anti-anginal agents.76 % of slow flow patients recieved at least two classes of anti anginals while 70 % of the normal flow patients received the same.Considering three classes of anti anginals it was 64 % for the slow flow group versus 32 % for the normal flow group.The difference in the proportion of patients on three classes of anti anginals between the two groups was statistically significant,(Table 4)

Table 4

MEDICATION CLASS VARIABLE	GROUP-I SLOW FLOW	GROUP-II NORMAL FLOW	P VALUE
ONE CLASS	57 (100%)	50 (100%)	0.76

TWO CLASSES	**44 (76%)**	**30 (70%)**	**0.64**
THREE CLASSES	**37 (64%)**	**16 (32%)**	**<0.01**

Number (%) of patients with at least one,two or three classes of anti anginal medication in current physician prescription – Nitrates,Beta Blockers,Calcium Channel Blockers,One Class – Nitrates alone,Two Classes – Nitrates and Beta Blockers or Calcium Channel Blockers,Three Classes – Nitrates,Beta Blockers and Calcium Channel Blockers.

5. Biochemical profile of study population :

The results of biochemical tests are depicted in Table 5.B.glucose was 98.7 ± 13.2 mg % for the slow flow group versus 95.6 ± 11.9 mg % for the normal flow group.Hemoglobin measured 12.8 ± 1.5 g % in the slow flow group and 12.3 ± 1.6 g % in the normal flow group.Lipid measurements were 127.8 ± 16.7 mg % versus 122.9 ± 18.5 mg % for LDL,44.9 ± 12.9 mg % versus 42.8 ± 13.6 mg % for HDL for the slow flow and normal flow groups respectively.Total Cholesterol was 192.7 ± 23.8 mg % for the slow flow group and 188.8 ± 43.7 mg % for the normal flow.Triglycerides measured 156.9 ± 23.8 mg % for slow flow and 153.7 ± 22.9 mg % for normal flow.The difference between the two sets of variables for the slow flow and normal flow groups was statistically insignificant.

Table 5

BIOCHEMICAL VARIABLE	GROUP-I SLOW FLOW	GROUP-II NORMAL FLOW	P VALUE
B.GLUCOSE	**98.7 ± 13.2**	**95.6 ± 11.9**	**0.43**
TOTALCHOLESTEROL	**192.7 ± 23.8**	**188.8 ± 43.7**	**0.56**
LDL-CHOLESTEROL	**127.8 ± 16.7**	**122.9 ± 18.5**	**0.86**
HDL-CHOLESTEROL	**44.9 ± 12.9**	**42.8 ± 13.6**	**0.76**
TRIGLYCERIDES	**156.9 ± 23.8**	**153.7 ± 22.9**	**0.75**
HEMOGLOBIN	**12.8 ± 1.5**	**12.3 ± 1.6**	**0.67**

All measurements on fasting venous blood samples

Values expressed in mg / 100mL

Hemoglobin values in g / 100mL

6. TMT profile of study population :

The various measures on TMT for the two groups are tabulated in Table 6.The difference in total work load and maximum exercise duration was statistically statistically between the two groups.While average total exercise duration was 346 ± 74 seconds in the slow flow it was 443 ± 72 seconds in the normal flow.Maximum workload between the two groups measured 9.8 ± 0.6 METS in the slow flow while it was 12.4 ± 0.4 METS in the normal flow group.The differences in various measures of ST depression were also statistically significant between the two groups except for the maximum amplitude of ST depression.The time to onset of ST depression was 329 ± 64 seconds in the slow flow group while it averaged 421 ± 73 seconds in the normal flow group.The time to offset of ST depression averaged 3.8 ± 0.7 seconds in the slow flow group while it averaged 2.5 ± 0.4 seconds in the normal flow group.The maximum ST depression was 1.4 ± 0.6 mm in the slow flow group and 2.5 ± 0.4 mm in the normal flow group.

Table 6

TMT PARAMETER VARIABLE	GROUP-I SLOW FLOW	GROUP-II NORMAL FLOW	P VALUE
TOTAL WORK LOAD	9.8 ± 0.6	12.3 ± 0.4	< 0.05
TOTAL EXE. DUR.	346 ± 74	443 ± 72	< 0.05
MAXIMUM ST ↓	1.4 ± 0.4	1.2 ± 0.2	0.51
TIME TO ONSET OF ST ↓	329 ± 64	421 ± 73	< 0.01
TIME TO OFFSET OF ST ↓	515 ± 26	390 ± 31	< 0.05

Total Work Load - in Metabolic Equivalents (METS) - mL/kg/minute,

Total Exe. Dur. - Total Exercise Duration in seconds,

Maximum ST↓- Maximum ST segment depression in millimeters,

Time to onset of ST↓ - Time to onset of ST segment depression in seconds,

Time to offset of ST↓ - Time to offset of ST segment depression in seconds

7.Follow-up events in the study population :

The follow-up events in the study population are depicted in Table 7 and Graph 1.The occurrence of angina was significantly greater in the slow flow group at 30 days follow up versus normal flow (46 % versus 30 %).The incidence of hospitalization for intractable angina was not significantly different between the two groups (5 % versus 4 %).

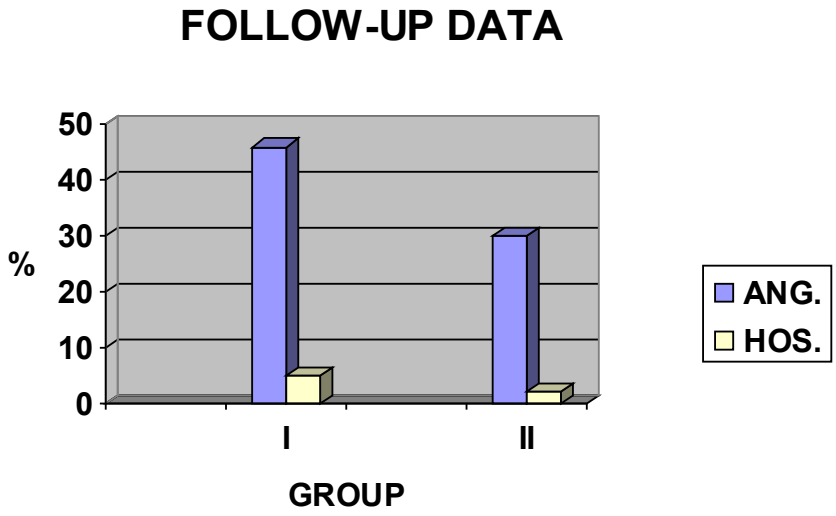
Table 7

FOLLOW-UP EVENT VARIABLE	GROUP-I SLOW FLOW	GROUP-II NORMAL FLOW	P VALUE
ANGINA	26(46%)	15(30%)	< 0.05
HOSPITALIZATION	3(5%)	2(4%)	0.35

Anginal episode

Hospitalization for Angina

All in the follow-up period



Graph 1

Follow-up data in Group I – Slow flow and Group II – Normal flow expressed as % of patients presented with Angina Pectoris / Hospitalization.
ANG. – Angina,HOSP. - Hospitalization

8.Incidence of NOCAD and CSFP :

The incidence of CAD patients with NOCAD was 5 % and that of CSFP 3% at our cardiovascular catheterization laboratory among patients undergoing CAG.

9. Angiographic Characteristics of slow flow group :

Relevant findings on angiography for the slow flow group are depicted in Tables 8-10. and Graphs 2-4.The mean CTFC was 51.3 ± 5.4 for LAD,36.9 ± 4.6 for LCX and 32.5 ± 3.3 for RCA.Mean CTFC for all the three vessels was 41.6 ± 5.7.The difference between the measures was statistically highly significant for the slow flow versus normal flow groups.21 % of the patients had 3 vessel

involvement in CSFP while 37 % and 42 % had involvement of 2 and 1 vessel respectively in CSFP.LAD was the commonest involved vessel seen in 67 % of slow flow patients followed by RCA at 59 % and finally LCX at 52 %.

Table 8

ANGIOGRAPHIC VARIABLE	GROUP-I SLOW FLOW	GROUP-II NORMAL FLOW	P VALUE
LAD / 1.7	51.3 ± 5.4	22.6 ± 1.7	< 0.001
LCX	36.9 ± 4.6	22.9 ± 2.3	< 0.001
RCA	32.5 ± 3.3	21.5 ± 2.8	< 0.001
Mctfc	40.3 ± 5.7	22.3 ± 3.6	< 0.001

LAD / 1.7 – CTFC of LAD, mCTFC – mean CTFC of LAD/1.7,LCX and RCA
All in number of cine-frames

Table 9

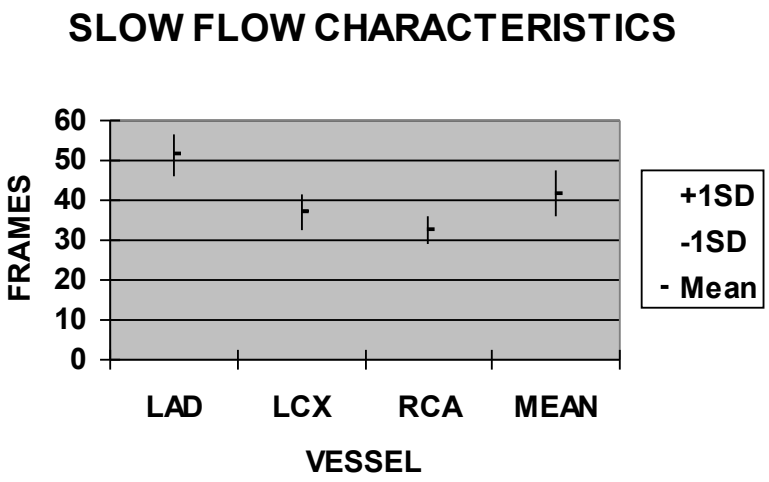
ANGIOGRAPHIC VARIABLE	GROUP-I SLOW FLOW
1 VESSEL	24 (42%)
2 VESSEL	21 (37%)
3 VESSEL	12 (21%)

At least 1,2 or 3 vessel involvement

Table 10

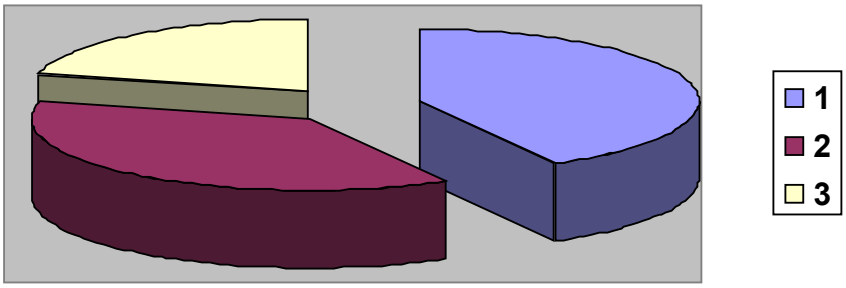
ANGIOGRAPHIC VARIABLE	GROUP-I SLOW FLOW
LAD	38 (67%)
RCA	34 (59%)
LCX	30 (52%)

Target vessel with CSFP



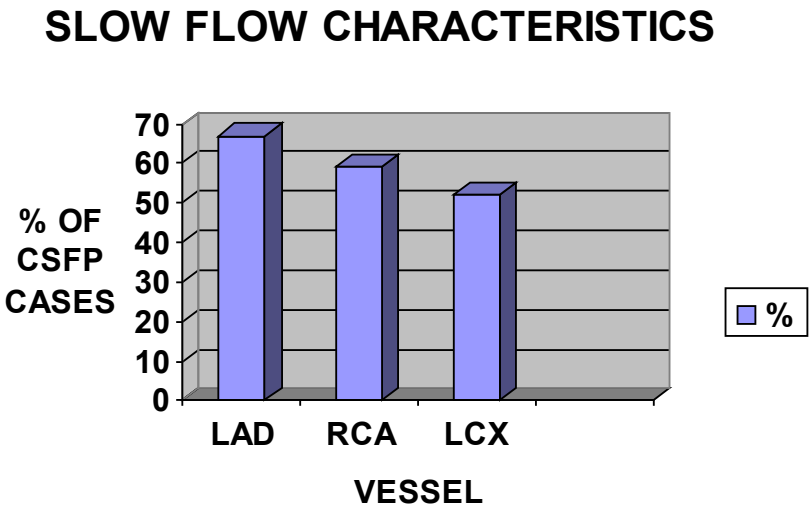
Graph 2

CTFC in number of frames expressed as Arithmetic mean ± 1 S.D. in each of the 3 vessels LAD,LCX and RCA,mean CTFC is displayed at the last.



Graph 3

Number of vessels involved in slow flow – At least 1,2 or 3 vessel involvement.



Graph 4

Percentage of slow flow cases with LAD,LCX and RCA involvement.

ILLUSTRATIVE CASE PROFILES

SLOW FLOW PROFILES

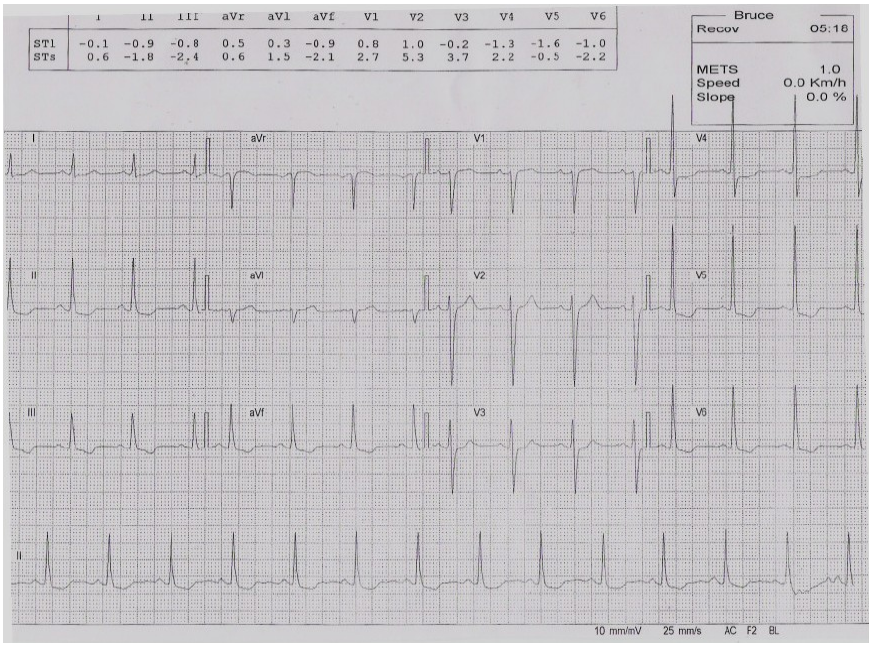
1) Mr.Nawab Jan / 55 / M / CAG No : 819 / 06 / MRD No : 862040

Smoker,Hypertensive,f/h of CAD +,

Recurrent angina on follow up,

On Nitrates,Beta blockers and Calcium Channel Blockers.

TMT profile



Total Work load 10.1 METS

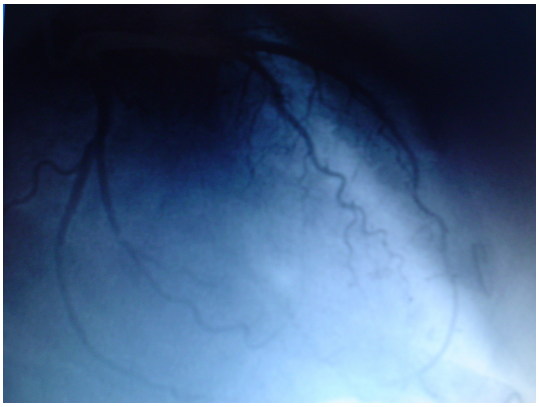
Total Exercise duration 411 s

Time to onset of ST ↓ 265 s

Time to offset of ST ↓ 532 s

CAG profile

CTFC OF LAD - FRAME 1



CTFC OF LAD - FRAME 56

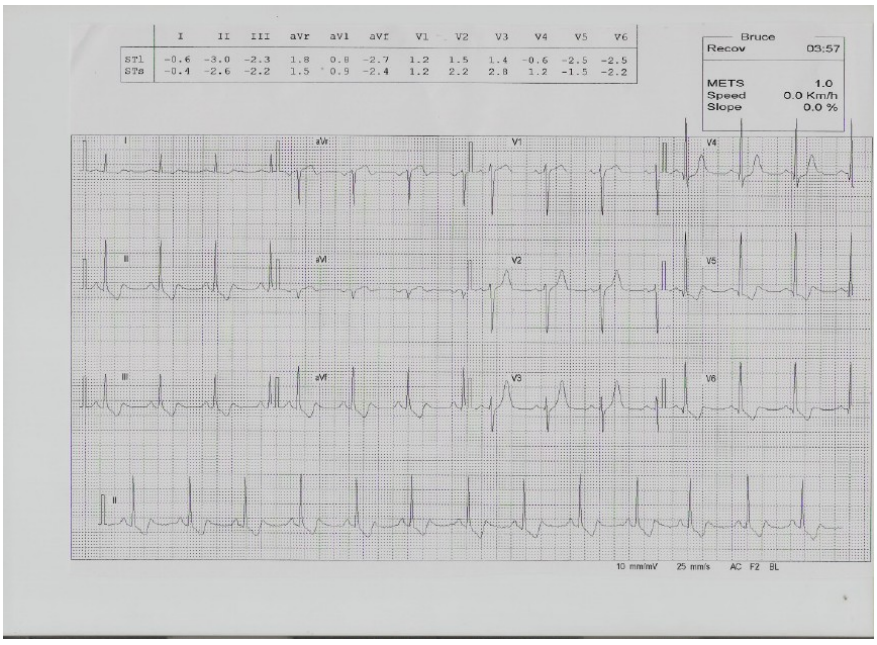
2)Mr.Shahul Hameed / 53 / M / MRD No : 853913

Hypertensive,f/h of CAD+

Recurrent Angina on follow up,

On Nitrates,Beta Blockers and Calcium Channel Blockers

TMT profile



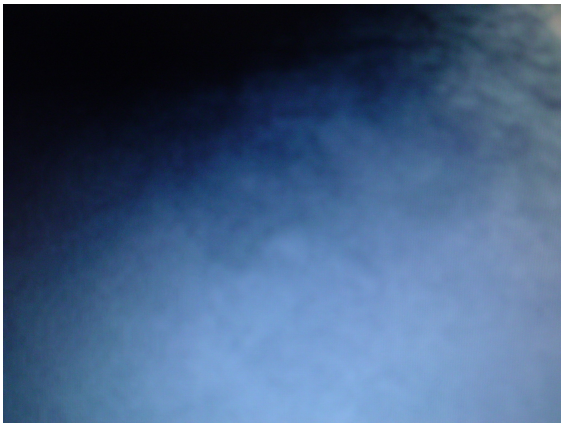
Total Work load 9.4 METS

Total Exercise duration 420 s

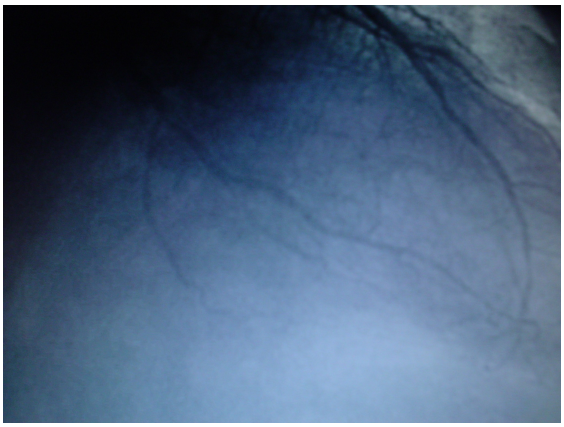
Time to onset of ST ↓ 258 s

Time to offset of ST ↓ 497 s

CAG profile



CTFC OF LCX - FRAME 1



CTFC OF LCX - FRAME 41

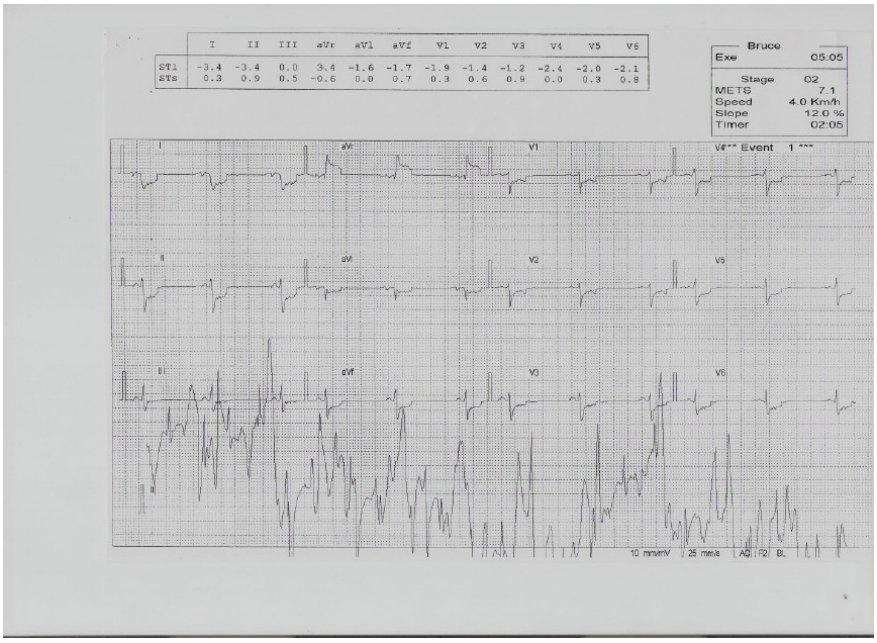
3)Mrs.Pathuma / 53 / F / MRD No : 844027

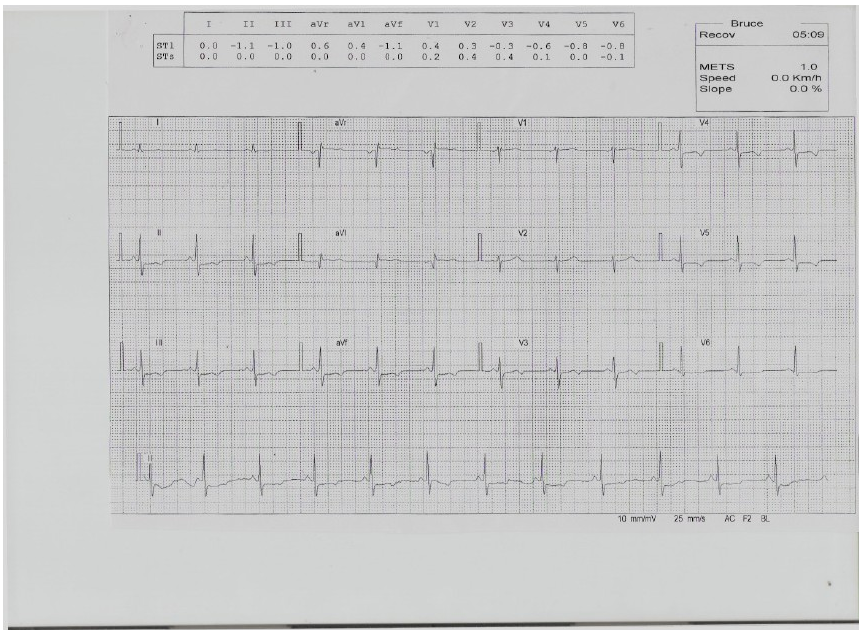
Smoker,Hypertensive,Dyslipidaemic,f/h of CAD +,

Recurrent angina on follow up,

On Nitrates,Beta blockers and Calcium Channel Blockers.

TMT profile





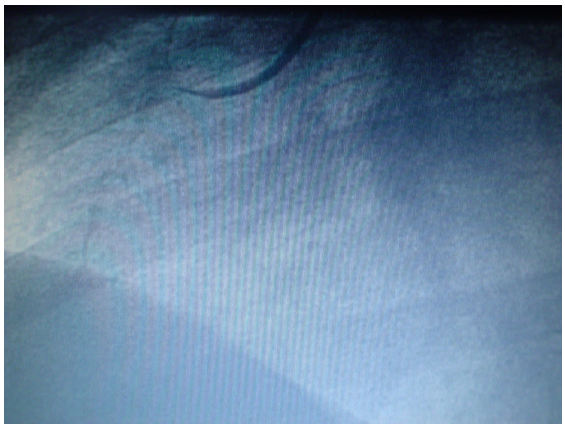
Total Work load 9.2 METS

Total Exercise duration 419 s

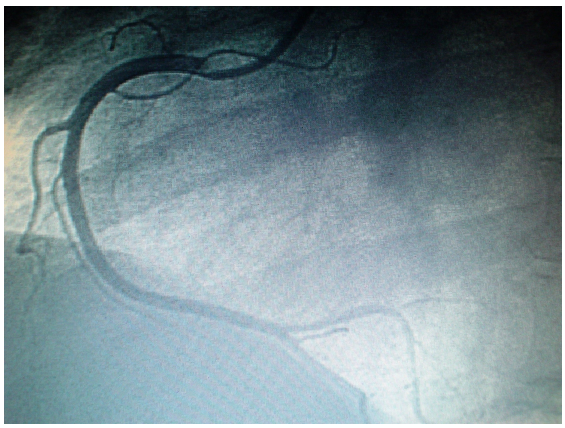
Time to onset of ST ↓ 354 s

Time to offset of ST ↓ 530 s

CAG profile



CTFC OF RCA - FRAME 1



CTFC OF RCA - FRAME 31

NORMAL FLOW PROFILE

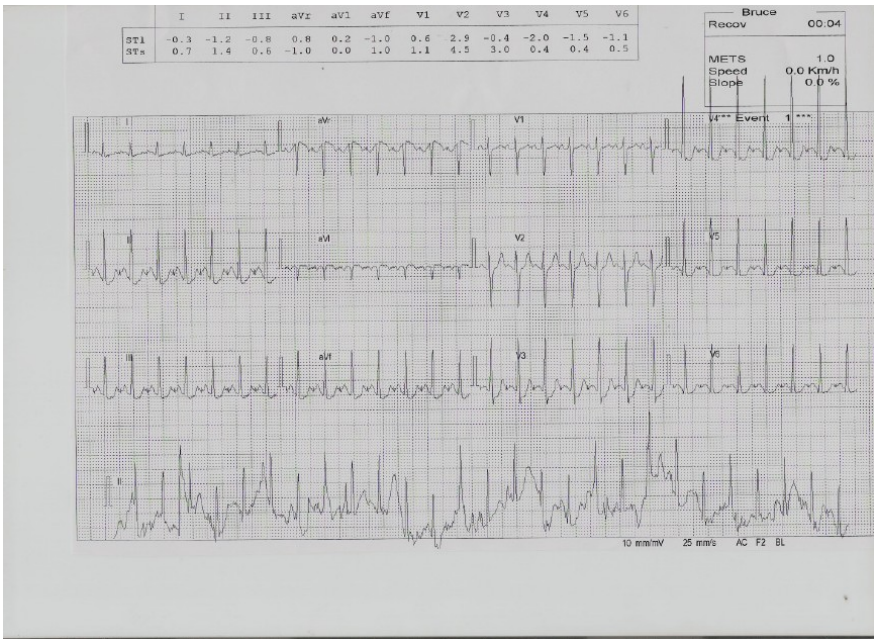
Mrs.Rajammal / 64 / F / MRD No : 857273

Diabetic,Dyslipidaemic

No recurrent angina on follow up,

On Nitrates.

TMT profile



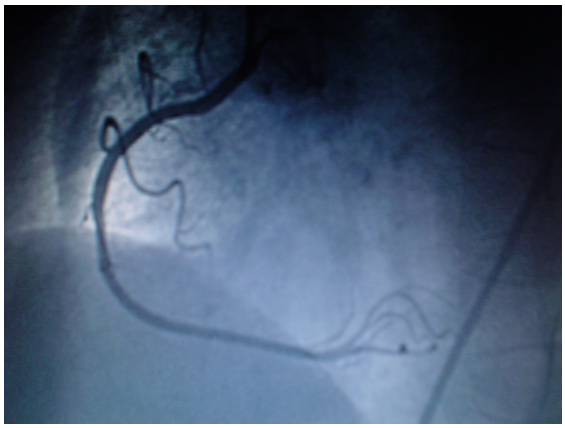
Total Work load 12.8 METS

Total Exercise duration 485 s

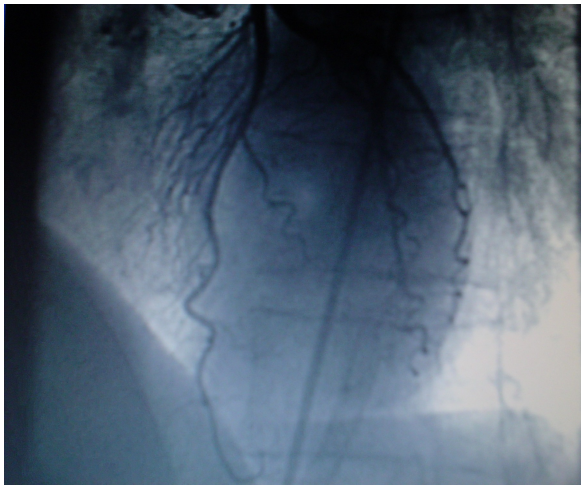
Time to onset of ST ↓ 354 s

Time to offset of ST ↓ 411 s

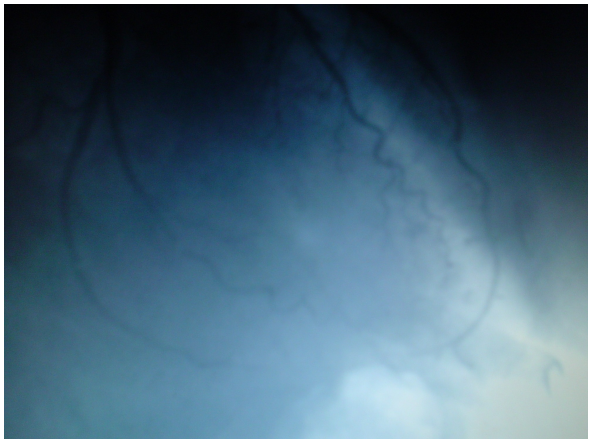
CAG profile



CTFC OF RCA - FRAME 18



CTFC OF LAD - FRAME 20



CTFC OF LCX - FRAME 20

DISCUSSION

Comparison with other Studies

There is a growing body of evidence that CSFP is a unique clinical subset in NOCAD characterized by delayed opacification of epicardial coronary arteries during selective coronary angiography in the absence of obstructive epicardial coronary disease.However consensus is lacking in the characterization of the same.

A.Mehta,R Passey,J P N Sawhney et al[58]reported that slow flow is more common in female patients. Females were younger than males by a decade in their study. Hypertension, diabetes mellitus, and dyslipidemia are more commonly associated in both females and males. Smoking is the commonest association in male patients. All the females were pre-menopausal.

On the other hand Falgun Panchal,Narendra S Tanwar,Sanjay C Shah et al[57] report that patients with slow flow are more likely to be men,diabetics with typical angina and positive stress test, and more likely to be on antianginals as compared to patients with normal coronaries.

Goel P K,Gupta S K,Agarwal A et al[56]concluded differently that CSFP patients constitute a definite subset within the wide spectrum of syndrome X and that the phenomenon of SCF could be used as a marker for myocardial ischemia.My contention is that Cardiac syndrome X and CSFP are mutually exclusive subsets of NOCAD.

Thus it is evident from the divergent conclusions of the above studies vis a vis my conclusions that CSFP has not been unambiguously characterized.There exists a scope for further accurate characterization of clinical profile and the natural history in CSFP at least in the Indian sub continent with its impending pandemic of CAD.

Several other studies have focused on different niche aspects of CSFP,but paucity of literature does not permit immediate comparisons nor definite conclusions regarding the study questions.

Ertin Yetkin,Hasan Turhan,A.Riza Erbay et al[62]state that patients with MI and NOCAD have higher TIMI frame counts for all coronary arteries when compared to patients without MI and NOCAD. Absence of difference between smokers and non-smoker in the myocardial infarction group in respect to TIMI frame count, has suggested that smoking does not lead to further increase of TIMI frame counts. On the other hand, in patients without MI and with NOCAD, smokers have higher TIMI frame counts than non-smokers have. Increased TIMI frame count of patients with MI and NOCAD has suggested that, whatever the real mechanism underlying this phenomenon, decreased coronary flow rate may be a common step in the pathogenesis of myocardial infarction with normal coronary arteries. Additionally, when considering the high percentage of smoking status without any increasing effect on TIMI frame count in myocardial infarction group, cigarette smoking can be considered as a triggering factor to initiate myocardial infarction.My study albeit different was similar in concluding that smokers are more likely to have CSFP in NOCAD patients.

As per the conclusions of Emrah Binak,Huseyin Gunduz,Muslum Sahin et al[60]There was no difference between slow

flow and normal flow with respect to age, fasting plasma glucose, triglyceride, total cholesterol, high density lipoprotein, low density lipoprotein, hemoglobin A1c, systolic–diastolic blood pressure levels, history of smoking and alcohol consumption.Plasma glucose at 2 h of oral glucose tolerance test was significantly higher in slow coronary flow patients compared to normal flow.In addition, the number of patients who met the criteria of impaired glucose tolerance was significantly higher in slow flow group.Their results suggest that impaired glucose tolerance may be an independent etiological factor for slow flow phenomenon.In my study diabetics and fasting blood glucose values were not significantly different between the slow flow and normal flow groups.

Dogan Erdogan,Mustafa Caliskan,Hakkan Gullu et al[59] state that demographic features, coronary risk factors and echocardiographic measurements except diastolic function

parameters and biochemical measurements are similar between the slow flow and normal flow groups.Coronary Flow Reserve values are significantly lower in subjects with CSFP than in the control group. In addition, TIMI frame count independently correlated with Coronary Flow Reserve.They suggested that Coronary Flow Reserve,which reflects coronary microvascular function, is impaired in patients with CSFP, and CTFC well correlates with Coronary Flow Reserve.I would prefer to treat microvascular angina and CSFP as two different exclusive subsets of NOCAD.

Sezgin AT,Topal E,Barutcu I et al[64]studied the echocardiographic features in patients with CSFP. There were no significant differences with respect to systolic parameters between the slow flow and normal flow groups; in spite of these, group I showed impaired left ventricular diastolic patterns compared to group II. Group I patients had higher peak late diastolic filling velocities due to enhanced atrial systole (A), lower peak (E/A) diastolic filling velocity ratios, and longer isovolumetric relaxation times compared with group II, and these were statistically significantIn conclusion; the authors detected diastolic filling abnormalities and showed diastolic dysfunction in patients with SCF.Echocardiographic evaluation was normal in both slow flow and normal flow groups in my study.

One contemporary study focused on the arrythmogenic potential of CSFP.Sait M.Dogan,Nesligul Yildirim,Metin Gursurer et al[63]state that there was no statistically significant difference between the slow flow and normal flow groups with respect to age,sex, hypertension, diabetes mellitus, hyperlipidemia, and cigarette smoking.P-wave dispersion and P-wave duration both were found to be greater in patients with slow flow than in normal flow marking its arrythmogenic potential for atrial fibrillation.All my study subjects however had a normal resting ECG.

Ergun Topal,Ramazan Ozdemir,Irfan Barutcu et al[61] studied the effects of short-term trimetazidine therapy on CSFP.They concluded that it improved Heart Rate Variability parameters and endothelial products such as Endothelin-1 and Nitric Oxide as well as anginal symptom in patients with SCFP. Trimetazidine was not prescribed to any of my study patients

The 3 % incidence of CSFP and 5% of NOCAD at our cardiovascular catheterization laboratory observed in my study was quite different from the varying reports of 1 % and 7 % reported by various investigators [5,6].

Generalization of Observation / Explanation for variation

A perusal of the above discussed original papers shows consistency of observation in certain spheres but discordance in others.I would like to attribute it to varying study populations and differing case inclusion/exclusion criteria.Furthermore the study population noted in the studies were not homogenous. The reference cut off for definition of slow flow versus normal flow also varied between studies and this could be an important contributor to the inconsistency in observations.

Study Highlights

This study is unique in that it addresses Coronary Slow Flow Phenomenon in a homogenous subset of stable CAD,that is NOCAD patients with no prior or current history of acute coronary syndrome.Objective parameters for diagnosing CAD were employed in all the study subjects eliminating the element of subjective bias in diagnosis.Stringent inclusion and exclusion criteria were employed to ensure that the conclusion of the study is not due to chance.Hitherto numerical values for slow flow in the individual coronary arteries with reference to the international reference range has not been published from the Indian sub continent,to the best of my knowledge.In addition currently there is no data available on comparison between various measures of ischaemia and functional capacity on TMT in NOCAD subsets from the Indian subcontinent.Emphasising on the South Indian population as a distinct ethnic group at a unique and great risk of CAD,this study humbly strives to throw some light on the “Coronary Slow Flow Syndrome”.

Study Limitations

Several limitations of this study have been kept in mind.

The follow-up of patients was for a period of 30 days only.More long term follow-up and possibly repeat coronary evaluation may be necessary to study the natural history of “Coronary Slow Flow Syndrome”.

The angiographic definition of normal coronary arteries relies on axial contrast angiograms of the vessel lumen which underestimate the presence of atherosclerotic plaque.A contributing factor to insensitivity of angiography for detection of plaques is that atherosclerosis is associated with medial atrophy and vessel wall dilatation resulting in diffusely diseased coronary arteries appearing to have angiographically normal lumen.Given the inherent limitation of angiography, it is not surprising that there is limited information about the true prevalence of plaques in patients with coronary artery disease and normal coronary arteries.IVUS overcomes the limitation of angiography with tomographic images which provide accurate characterization of vessel lumen and wall geometry, as well as the presence and distribution of atherosclerotic plaques.These advantages mean that IVUS is the most sensitive technique for detecting the presence of coronary atherosclerosis in patients with coronary artery disease and angiographically normal coronary arteries.However,I did not have the opportunity to perform IVUS.

Another potential limitation of the study is precisely unknown etiology of angina pectoris. Although I have excluded patients with valvular heart disease, atrial fibrillation, infective endocarditis, vasculitis and hematological disease in order to eliminate potential embolic source, the exact mechanism of chest pain with normal coronary angiogram and slow flow is still unclear. Acute myocarditis, particularly of infectious origin (Coxsackie virus), may simulate CAD in patients with normal coronary arteries. Atrial myxoma, and mitral valve prolapse has been implicated as a potential cause of angina pectoris with normal coronary arteries, which may be true in an exceedingly small number of patients.

Prior studies have shown that the volume, rate and pressure of the contrast injection as well as the coronary catheter size have little effect on the frame count.Because the timing, volume and pressure

of the contrast injection were not controlled in the study, this probably would introduce a random amount of error into my measurement of frame count. Although there are significant associations between CTFC and certain clinical and hemodynamic variables such as BP,PR, gender,BSA, and age, the absolute change in frame count is fairly small. And these differences may be important when establishing the normal CTFC value.

CONCLUSION

Conclusions from this study are :

1.Non Obstructive Coronary Artery Disease has an incidence of 5 % among patients undergoing Coronary Angiography.

2.Coronary Slow Flow Phenomenon has an incidence of 3 % among patients undergoing Coronary Angiography.

3.Non Obstructive Coronary Artery Disease with Coronary Slow Flow Phenomenon is more prevalent among males as compared to females,they are more likely to be smokers and hypertensive with a family history of Coronary Artery Disease.

4.Non Obstructive Coronary Artery Disease patients with Coronary Slow Flow Phenomenon achieve comparatively a lesser work load,have a shorter total exercise duration with an earlier onset and a later offset of ST depression on Tread Mill Test.

5.Coronary Slow Phenomenon is commonest in a single coronary artery with an incidence of 47 % and the Left Anterior Descending Coronary Artery is the most commonly affected vessel at 68 % incidence in Non Obstructive Coronary Artery Disease.

6.Coronary Slow Flow Phenomenon is characterized by a CTFC of 51.3 ± 5.4 frames for LAD,36.9 ± 4.6 frames for LCX , 32.5 ± 3.3 frames for RCA and a mean CTFC for all the three coronary vessels of 41.6 ± 5.7 frames in an urban South Asian Population with Non Obstructive Coronary Artery Disease,The CTFC values are similar to the figures published internationally in the literature incorporating varying populations of different ethnic origins.Hence Corrected TIMI Frame Count can be a universally applicable tool in segregating Non Obstructive Disease patients in to slow flow and normal flow sub-sets.

7.Non Obstructive Coronary Artery and Coronary Slow Flow Phenomenon is correlated with an adverse clinical outcome – these patients have recurrent anginal episodes on out-patient follow up and are more likely to require combination therapy with at least three different classes of anti-anginal medications for better anginal relief and improved quality of life.

On the basis of the above conclusion the study hypothesis that "Coronary Slow Flow Phenomenon" in Non Obstructive Coronary Artery Disease indeed represents a novel disease entity aptly to be termed the"Coronary Slow Flow Syndrome" is proved true.

Scope for further exploration in "Coronary Slow Flow Syndrome":

"Coronary Slow Flow Syndrome" is still inadequately characterized and its natural history remains unclear.A larger study with a greater number of patients and a longer duration of follow up should throw more light on the same.

Further more a lot of work needs to be done on the Echocardiographic and Biochemical characteristics of "Coronary Slow Flow Syndrome."This could eventually help in better understanding of the aetiopathogenesis,defining better anti-anginal regimens and ultimately help improve patient care.

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GLOSSARY OF ABBREVIATIONS & ACRONYMS

APS	ANGIOGRAPHY PERFUSION SCORE
MPG	MYOCARDIAL PERFUSION GRADE
BP	BLOOD PRESSURE
NOCAD	NON-OBSTRUCTIVE CORONARY ARTERY DISEASE
BSA	BODY SURFACE AREA
OM	OBTUSE MARGINAL BRANCH
CAD	CORONARY ARTERY DISEASE
PLV	POSTERO-LATERAL VENTRICULAR BRANCH
CAG	CORONARY ANGIOGRAM
PR	PULSE RATE
CCS	CANADIAN CARDIOVASCULAR SOCIETY
RCA	RIGHT CORONARY ARTERY
CFR	CORONARY FLOW RESERVE
S	Second
CSFP	CORONARY SLOW PHENOMENON
TIMI	THROMBOLYSIS IN MYOCARDIAL INFARCTION
(C)TFC	(CORRECTED) TIMI FRAME COUNT
TMPG	TISSUE MYOCARDIAL PERFUSION GRADE
ECG	ELECTROCARDIOGRAM
TPG	TIMI PERFUSION GRADE
ECHO	ECHOCARDIOGRAM
FFR	FRACTIONAL FLOW RESERVE
fps	frames per second
IVUS	INTRAVASCULAR ULTRASOUND
LAD	LEFT ANTERIOR DESCENDING
LCX	LEFT CIRCUMFLEX
METS	METABOLIC EQUIVALENTS
m	Minute
mm	Millimeter

SPECIMEN PROFORMA

"CORRECTED TIMI FRAME COUNT IN CORONARY SLOW FLOW PHENOMENON"

A SHORT-TERM FOLLOW-UP STUDY

DEMOGRAPHIC DATA

NO :

NAME :

AGE : SEX :

MARITAL STATUS :

EDUCATIONAL LEVEL :

OCCUPATION/INCOME :

CD NO : IP NO :

ETHNICITY :

HISTORY

CHEST PAIN PALPITATION

DYSPNOEA

SYNCOPE

RISK FACTOR ASSESSMENT

HYPERTENSION OBESITY

DYSLIPIDAEMIA FAMILY HISTORY

FAMILY HISTORY

DIABETES

SMOKING : PACK YEARS

PHYSICAL EXAMINATION

GENERAL EXAMINATION

BODY MASS INDEX kg/m^2

OTHERS

CARDIOVASCULAR EXAMINATION

VENOUS & LYMPHATIC SYSTEM

JVP cm H_2O OTHERS

WAVEFORM

ARTERIAL SYSTEM

PERIPHERAL PULSATION OTHERS

BLOOD PRESSURE mm Hg

HEART

INSPECTION / PALPATION / PERCUSSION / AUSCULTATION

OTHER SYSTEMS

INVESTIGATIONS

BLOOD BIOCHEMISTRY

LIPID PROFILE

COMPLETE BLOOD COUNT

RESTING ELECTROCARDIOGRAM (ECG)

ECHOCARDIOGRAM (ECHO)

COMPLETE CLINICAL DIAGNOSIS

MEDICATIONS

NITRATES YES / NO

BETA-BLOCKERS YES / NO

CALCIUM CHANNEL BLOCKERS YES / NO

TREADMILL TEST (TMT)

TMT No : Date of procedure : Protocol :

Total Workload : METS

Total Exercise duration : seconds

Time to onset of ST segment depression : seconds

Maximum ST segment depression : mm

Time to offset of ST depression in to recovery : seconds

CORONARY ANGIOGRAPHY(CAG)

CAG No: Date of procedure :

Technique : Medications :

Catheters used : Approach :

Contrast medium :

TARGET VESSEL	CORRECTED TIMI FRAME COUNT (FPS) / 12.5 × 30
LAD / 1.7	
LCX	
RCA	

RESULT

Coronary flow status : LAD/1.7 FPS Slow / Normal flow

LCX FPS Slow / Normal flow

RCA FPS Slow / Normal flow

Mean CTFC = { (LAD/1.7 + LCX + RCA) / 3 } FPS

REFERENCE RANGE[51]		**SLOW FLOW**[51]
LAD/1.7	**21.1 ± 1.5 frames**	**> 24.3 frames**
LCX	**22.2 ± 4.1 frames**	**> 30.4 frames**
RCA	**20.4 ± 3.0 frames**	**> 26.4 frames**

FOLLOW-UP

Anginal episode : Yes / No

Hospitalization for angina : Yes / No

DATA CHARTS **1.CLINICAL,HEMODYNAMIC AND BIOCHEMICAL DATA – STUDY GROUP (I)**

SERIAL NO :	NAME	SEX	AGE	SHT	DM	DYSLIP.	F.HIST.	SMOK.	BMIkg/m^2	BP PR	A.A	TC mg%	LDL mg%	HDL mg %
1	BABU	M	62	Y	Y	Y	Y	Y	24.5	128/80 65	3	169	111	32
2	PALANI	M	57	Y	Y	Y	Y	Y	32.7	126/84 68	3	216	144	58
3	SESHADRI	M	59	Y	Y	Y	Y	Y	26.9	134/90 72	3	172	126	46
4	PARASU	M	48	Y	Y	Y	Y	Y	24.8	130/86 70	3	187	135	48
5	BASHA	M	52	Y	Y	Y	Y	Y	26.5	128/88 71	3	211	142	57
6	LEELA	F	55	Y	Y	Y	Y	N	28.7	124/86 72	3	210	143	53
7	ELUMALAI	M	59	Y	Y	Y	Y	Y	28.8	128/84 74	3	174	138	54

8	RAJI	F	62	Y	Y	Y	N	N	31.6	126/82 70	3	216	140	51
9	ROSY	F	64	Y	Y	Y	N	N	32.4	138/72 68	3	210	142	48
10	PREMALATHA	F	67	Y	Y	Y	N	N	31.6	128/76 70	3	201	145	32
11	THANGARAJ	M	66	N	Y	N	N	Y	31.5	126/78 70	3	209	142	36
12	CHELLAM	M	39	Y	Y	N	N	Y	32.6	124/82 74	3	210	116	37
13	VADIVAMMAL	F	42	Y	Y	N	N	N	31.7	126/84 70	3	212	121	50
14	SARAVANAN	M	46	Y	Y	Y	N	Y	32.4	124/78 66	2	214	124	54

15	PERUMAL	M	62	Y	Y	Y	N	Y	31.7	128/80 68	2	215	126	56
16	NAGAMALAR	F	59	N	Y	Y	Y	N	31.5	126/84 71	2	216	137	38
17	SHAHUL	M	53	Y	N	Y	Y	N	24.6	120/84 74	3	210	138	40
18	PATHUMA	F	53	Y	N	Y	Y	N	26.8	124/84 75	3	208	142	42
19	NAWAB	M	55	Y	N	N	Y	Y	28.8	140/90 74	3	209	128	44
20	YAKOUB	M	35	Y	N	N	N	Y	27.9	140/82 74	3	178	134	47
21	MANOHARAN	M	47	Y	Y	N	N	Y	28.8	136/86 78	3	198	142	52
22	SRINIVASAN	M	45	Y	Y	Y	Y	Y	31.6	134/92 74	3	178	141	55
23	SIVARAMAN	M	48	N	Y	Y	Y	Y	28.8	140/80 68	3	185	138	56
24	GOVINDASAMY	M	52	Y	Y	Y	Y	Y	26.8	136/84 68	3	188	139	33
25	KISHORE	M	62	Y	Y	Y	Y	Y	25.8	130/80 66	3	190	141	35
26	ABDUL AZIZ	M	55	Y	Y	Y	Y	Y	27.8	128/84 66	3	192	128	36
27	SHABAN	M	61	Y	Y	Y	Y	Y	30.6	132/86 64	3	198	131	42
28	CHITTI BABU	M	57	Y	Y	Y	Y	Y	31.7	136/84 74	3	200	135	44
29	SELVAM	M	58	N	Y	Y	Y	Y	32.4	138/90 70	3	210	138	46
30	SELVA KUMAR	M	56	Y	Y	Y	Y	Y	30.8	134/84 70	3	212	139	55
31	MURUGAN	M	55	Y	Y	Y	Y	Y	26.8	130/82 72	3	214	141	56
32	ROBERT	M	48	Y	Y	Y	Y	Y	28.9	130/86 74	3	213	125	35
33	MASIMA	F	61	Y	Y	Y	Y	N	29.9	128/82 75	3	216	138	38
34	SAVITHA	F	49	Y	Y	Y	Y	N	30.5	130/84 72	3	178	118	39
35	CHANDRA	F	53	Y	Y	Y	Y	N	31.8	128/82	2	187	114	41

										76				
36	MANOHARAN	M	54	Y	Y	Y	Y	Y	31.7	130/84 74	2	198	129	44
37	MOHAN	M	63	Y	Y	Y	Y	Y	28.6	130/90 74	3	199	135	46
38	GOVND REDDY	M	55	Y	Y	Y	Y	Y	31.6	130/84 74	3	174	133	54
39	CHINATHAMBY	M	53	Y	Y	Y	Y	Y	28.8	128/86 72	3	175	134	37
40	SAROJA	F	54	Y	Y	Y	Y	N	30.6	128/90 74	3	177	137	38
41	JAYA	F	49	Y	Y	Y	Y	Y	29.6	130/84 74	3	178	135	47
42	LAKSHMI	F	37	Y	Y	Y	Y	N	25.6	130/84 72	3	179	141	54
43	DEVAKI	F	38	Y	N	N	N	N	26.8	126/86 74	2	186	141	55
44	MAHENDRAN	M	42	Y	N	N	N	Y	29.8	128/90 74	2	188	138	35
45	VEERAMAL	F	48	Y	N	N	N	N	28.6	126/86 76	1	189	121	36
46	KANAGARAJ	M	46	Y	N	N	N	Y	29.5	128//9 2 68	1	191	126	37
47	RANGASAMY	M	49	Y	N	N	N	Y	30.8	130/92 72	1	174	129	39
48	ARUMUGAM	M	52	N	N	N	N	Y	31.6	130/92 74	1	175	135	56
49	SANKAR	M	59	N	N	N	N	Y	30.5	130/90 74	1	176	138	57
50	KANI	M	58	N	N	N	N	Y	31.6	128/90 72	1	177	132	38
51	MOHIDEEN	M	56	N	N	N	N	Y	30.2	126/92 74	1	178	141	43
52	KRISHNAN	M	48	N	N	N	N	Y	31.3	130/78 74	1	198	118	44
53	VASANTH	M	39	N	N	N	N	Y	30.7	136/72 68	1	199	124	48
54	RAJ MOHAN	M	36	N	N	N	N	N	31.5	134/90 70	1	200	129	56
55	ASOKAN	M	38	N	N	N	N	N	29.5	136/86 68	1	179	138	54
56	GEORGE	M	42	N	N	N	Y	Y	30.6	134/78 66	1	189	141	55
57	HARI	M	49	Y	N	N	Y	Y	28.8	136/78 69	1	194	142	53

Legend : SHT-Systemic Arterial Hypertension,DM-Diabetes Mellitus,DYSLIP.-Dyslipidaemia,F.Hist.-Family History of CAD,SMOK.-Active & Current Smoking History,Y - Present,N - Absent,BMI-Body Mass Index,PR-Pulse Rate,BP- Blood Pressure in mmHg,A A – At least 1,2 or 3 classes of anti-anginals- Nitrates,Beta blockers,Calcium channel blockers,TC- Total Cholesterol,LDL- Low Density

Cholesterol,HDL-High Density Cholesterol,TGL-Triglycerides,B.GLU.- Blood Glucose, (All on fasting venous samples).

CLINICAL,HEMODYNAMIC AND BIOCHEMICAL DATA – CONTROL GROUP (II)

SERIAL NO:	NAME	SEX	AGE	SHT	DM	DYSLIP.	F.HIST.	SMOK.	BMI kg/m^2	BP PR	AA	TC mg%	LDL mg%	HDL mg%
1	RAJAMMAL	F	64	N	Y	Y	N	N	24.8	120/76 74	1	145	105	29
2	RAVI	M	68	Y	N	Y	Y	Y	31.6	120/80 78	3	233	142	56
3	RAMALINGAM	M	69	Y	N	Y	Y	Y	24.9	138/79 86	2	165	109	32
4	MANICK	M	42	Y	Y	Y	N	Y	26.6	130/84 90	3	230	140	34
5	RAGUNATHAN	M	41	Y	Y	Y	Y	Y	30.5	126/84 76	2	228	138	36
6	MAHADEVI	F	46	Y	Y	Y	N	N	31.2	128/82 78	3	167	141	48
7	SEETHALAKSHMI	F	52	Y	Y	Y	Y	N	30.6	136/76 65	3	176	106	51
8	KUPPAN	M	53	Y	Y	Y	N	Y	31.4	130/90 78	3	198	112	54
9	RAMAKRISHNAN	M	58	Y	Y	Y	Y	Y	29.8	122/78 65	3	225	114	55
10	DEVA DAN	M	48	Y	N	Y	Y	Y	30.6	126/86 78	3	230	115	53
11	SURESH	M	47	Y	N	N	Y	Y	31.4	136/88 78	3	228	139	32
12	JAYACHANDRAN	M	56	N	Y	Y	N	Y	30.7	130/74 66	2	167	134	34
13	USHA	F	54	N	Y	Y	N	N	28.8	120/74 65	3	168	137	38
14	RAMASAMY	M	53	N	Y	Y	Y	Y	25.2	122/76 68	3	194	129	47
15	MANOHARAN	M	58	N	N	Y	Y	Y	26.8	124/78 66	3	187	132	46
16	VISALAKSHI	F	59	Y	Y	Y	Y	N	28.8	128/76 78	2	183	140	44
17	RAJALAKSMI	F	65	Y	Y	Y	Y	N	30.4	120/776 90	3	185	122	48
18	VEERARAJAN	M	66	Y	Y	Y	Y	Y	26.6	124/86	2	210	127	52

										76				
19	RAGAVAN	M	62	Y	N	N	Y	Y	30.4	122/86 80	3	213	109	54
20	MOHAN	M	48	Y	Y	Y	Y	Y	30.4	136/76 76	2	224	111	38
21	SUBRAMANI	M	59	Y	Y	Y	N	Y	29.6	124/82 78	3	226	132	45
22	SATHYAMURTHY	M	68	Y	Y	Y	Y	Y	25.8	134/88 66	2	228	127	51
23	SYED	M	69	Y	N	N	N	Y	28.8	136/76 78	3	231	140	47
24	MOHD. IQBAL	M	64	Y	Y	Y	Y	Y	29.6	132/74 78	2	159	119	36
25	MURUGAN	M	58	Y	Y	N	Y	Y	27.8	136/76 74	3	164	134	38
26	DHANDAYUDHAM	M	55	Y	Y	Y	Y	Y	25.6	132/90 79	2	224	118	44
27	GOWRI	F	54	Y	N	N	Y	N	27.8	136/90 78	2	228	132	46
28	RAJESH	M	53	Y	Y	Y	Y	Y	30.2	134/78 79	2	231	124	48
29	VEERASAMY	M	54	Y	Y	Y	N	Y	29.6	122/88 68	2	178	127	53
30	SAROJA DEVI	F	56	Y	Y	Y	N	N	25.8	126/76 68	2	188	132	47
31	GAYATHRI	F	58	Y	N	N	Y	N	26.8	130/88 78	2	205	108	46
32	CHITRA	F	48	N	Y	Y	Y	N	30.4	132/74 76	1	231	106	35
33	BACKYAM	F	47	N	Y	N	N	N	28.8	124/76 66	1	167	141	38
34	DEIVANI	F	52	N	N	Y	N	N	30.4	128/78 68	1	178	135	47
35	RANI	F	53	Y	Y	N	N	N	28.2	132/90 78	1	223	138	52
36	GOWRI	F	61	Y	Y	Y	N	N	28.6	134/86 78	1	209	140	53
37	KALYANI	F	60	N	Y	N	N	N	24.8	120/90 78	1	212	129	34
38	SARASWATHY	F	62	N	N	Y	N	N	26.4	122/88 86	1	225	131	43
39	MARIAMMAL	F	58	N	Y	Y	N	N	26.2	126/88 79	1	230	118	51
40	KANAMMA	F	59	N	Y	N	N	N	28.9	120/80 75	1	148	121	54
41	CHANDRAKALA	F	63	N	N	N	N	N	27.6	124/84 78	1	159	126	29
42	PAVAI	F	66	N	Y	N	N	N	28.4	128/86	1	168	129	33

										78				
43	ANJALAKSHI	F	61	N	Y	N	N	N	26.4	132/88 76	1	182	138	37
44	THANGAMMAL	F	64	N	Y	N	N	N	27.2	128/80 78	1	189	141	41
45	LALITHA	F	55	N	N	N	N	N	25.6	130/78 76	1	176	138	45
46	KOKILA	F	58	N	Y	N	N	N	26.8	122/90 68	1	184	135	48
47	MARIAMML	F	59	N	N	N	N	N	27.4	124/86 76	1	206	136	42
48	CHANDRA	F	54	N	N	N	N	N	26.8	126/88 78	1	209	140	43
49	JAYA	F	56	N	N	N	N	N	29.6	124/78 78	1	231	119	47
50	MARIAMMA	F	54	N	Y	Y	N	N	31.4	136/78 88	1	224	123	52

Legend: SHT-Systemic Arterial Hypertension,DM-Diabetes Mellitus,DYSLIP.-Dyslipidaemia,F.Hist.-FamilyHistoryof CAD,SMOK.- Active & Current Smoking History, Y - Present, N - Absent,BMI-Body Mass Index,PR-Pulse Rate,BP Blood Pressure in mmHg,A A - At least 1,2 or 3 classes of Anti-anginals - Nitrates,Beta blockers,Calcium channel blockers,TC-Total Cholesterol,LDL-Low Density Cholesterol,HDL-High Density Cholesterol,TGL-Triglycerides,B.GLU-Blood Glucose,(All on fasting venous samples).

2. TMT DATA – STUDY GROUP (I)

SER. NO:	TMTNO:	NAME/SEX/AGE	METS	EX.DUR s	MAX. ST ↓ mm	ONSET OF ST ↓ s
1	986	BABU/M/62	9.2	272	1.0	265
2	998	PALANI/M/57	10.4	420	1.5	393
3	943	SESHADRI/M/59	9.8	296	1.2	272
4	864	PARASU/M/48	10.1	414	1.4	282
5	798	BASHA/M/52	10.4	299	1.0	365
6	984	LEELA/F/55	9.5	386	1.8	386
7	785	ELUMALAI/M/59	9.8	376	1.8	277
8	675	RAJI/F/62	10.3	398	1.6	268
9	993	ROSY/F/64	10.2	403	1.5	277

10	567	PREMALATHA/F/67	10.1	419	1.4	272
11	669	THANGARAJ/M/66	9.4	365	1.8	287
12	845	CHELLAM/M/39	9.3	378	1.0	265
13	876	VADIVAMMAL/F/42	9.8	389	1.8	393
14	887	SARAVANAN/M/46	9.9	398	1.8	287
15	834	PERUMAL/M/62	10.0	412	1.0	298
16	862	NAGAMALAR/F/59	10.1	413	1.8	388
17	876	SHAHUL/M/53	10.3	416	1.6	386
18	784	PATHUMA/F/53	10.4	418	1.5	376
19	765	NAWAB/M/55	10.1	415	1.8	399
20	587	YAKOUB/M/35	10.1	416	1.8	382
21	934	MANOHARAN/M/47	9.2	378	1.8	276
22	987	SRINIVASAN/M/45	9.3	386	1.7	298
23	921	SIVARAMAN/M/48	9.5	384	1.6	391
24	989	GOVINDSAMY/M/52	9.6	382	1.0	265
25	945	KISHORE/M/62	10.4	412	1.7	393
26	976	ABDUL AZIZ/M/55	10.2	416	1.8	265
27	893	SHABAN/M/61	9.8	356	1.9	386
28	761	CHITTI BABU/M/57	9.8	348	1.0	265
29	439	SELVAM/M/58	10.2	411	1.0	393
30	931	SELAKUMAR/M/56	10.1	414	1.5	277
31	549	MURUGAN/M/55	10.2	416	1.2	386
32	785	ROBERT/M/48	10.3	415	1.3	272
33	874	MASIMA/F/61	10.2	405	1.4	392
34	762	SAVITHA/F/49	10.0	408	1.5	288
35	872	CHANDRA/F/53	10.3	411	1.6	278
36	756	MANOHARAN/M/54	9.2	387	1.7	299
37	919	MOHAN/M/63	9.3	395	1.8	272
38	566	GOVIND REDY/M/55	9.6	389	1.7	277
39	654	CHINTHAMBY/M/53	9.8	397	1.8	391
40	887	SAROJA/F/54	9.8	394	1.8	278
41	844	JAYA/F/49	9.9	394	1.0	391
42	643	LAKSHMI/F/37	10.2	412	1.7	279
43	771	DEVAKI/F/38	10.3	414	1.5	285
44	663	MAHENDRAN//42	10.3	411	1.6	393
45	343	VEERAMAL/F/48	10.1	418	1.7	286
46	221	KANAGARAJ/M/46	10.0	419	1.7	390
47	116	RANGASAMY/M/49	9.8	376	1.8	290
48	185	ARUMUGAM/M/52	9.8	387	1.8	299
49	335	SANKAR/M/59	10.1	411	1.9	391
50	339	KANI/M/58	10.4	411	1.0	386
51	556	MOHIDEEN/M/56	10.4	412	1.0	385
52	531	KRISHNAN/M/48	10.1	411	1.0	291

53	513	VASANTH/M/39	10.3	412	1.0	299
54	389	RAJ MOHAN/M/36	10.2	417	1.4	386
55	901	ASOKAN/M/38	10.2	420	1.6	390
56	1450	GEORGE/M/42	10.3	420	1.6	391
57	1323	HARI/M/49	10.4	419	1.8	298

Legend : METS- Total Work load in Metabolic Equivalents,EX.DUR.-Total Exercise Duration in seconds,MAX.ST↓-Maximum ST segment depression,ONSET OF ST↓-Time to onset of ST segment depression in seconds,OFFSET OF ST↓- Time to offset of ST segment depression in seconds.

TMT DATA – CONTROL GROUP (II)

SER. NO:	TMT NO:	NAME/SEX/AGE	MET	EX.DUR. s	MAX. ST ↓ mm	ONSET OF ST
1	1329	RAJAMMAL/F/64	11.9	371	1.0	348
2	1236	RAVI/M/68	12.7	515	1.4	494
3	1189	RAMALINGAM/M/69	11.9	386	1.0	484
4	1330	MANICK/M/42	12.4	513	1.2	356
5	1176	RAGUNATHAN/M/41	12.6	398	1.3	358
6	1098	MAHADEVI/F/46	12.1	468	1.4	486
7	1099	SITHALAKSHMI/F/52	12.7	508	1.0	490
8	1176	KUPPAN/M/53	12.5	512	1.0	351
9	1278	RAMKRSHNAN/M/58	11.9	367	1.0	355
10	1345	DEVA DAN/M/48	12.4	378	1.2	368
11	1323	SURESH/M/47	12.4	489	1.4	492
12	1332	JAYCHNDRAN/M/56	12.5	376	1.3	493
13	1285	USHA/F/54	11.9	371	1.2	494
14	1275	RAMASAMY/M/53	12.7	515	1.1	348
15	1260	MANOHARAN/M/58	11.9	386	1.3	490
16	1263	VISALAKSHI/F/59	12.4	514	1.4	491
17	1264	RAJALAKSHMI/F/65	12.6	398	1.0	358
18	1248	VEERARAJAN/M/66	12.6	423	1.0	378
19	1243	RAGAVAN/M/62	12.5	458	1.3	398

20	1290	MOHAN/M/48	11.9	513	1.3	487
21	1276	SUBRAMANI/M/59	12.4	512	1.4	490
22	1338	SATHYMRTHY/M/68	12.5	386	1.3	486
23	1305	SYED/M/69	12.6	389	1.4	367
24	1308	MOHD.IQBAL/M/64	12.6	514	1.3	389
25	1409	MURUGAN/M/58	12.5	512	1.4	490
26	1425	DHANDYUDHM/M/55	11.9	389	1.4	491
27	1472	GOWRI/F/54	12.6	377	1.4	398
28	1077	RAJESH/M/53	12.5	515	1.0	490
29	1177	VEERASAMY/M/54	12.7	378	1.3	494
30	1231	SAROJA DEVI/F/56	12.2	514	1.4	348
31	1188	GAYATHRI/F/58	12.4	386	1.2	367
32	1099	CHITHRA/F/48	12.5	387	1.2	490
33	1232	BACKYAM/F/47	12.7	398	1.1	356
34	1222	DEIVANI/F/52	12.0	514	1.0	371
35	1333	RANI/F/53	11.9	514	1.0	378
36	1201	GOWRI/F/61	12.1	398	1.0	490
37	1094	KALYANI/F/60	12.4	390	1.1	490
38	1087	SARASWATHY/F/62	12.6	377	1.2	486
39	1045	MARIAM/F/58	11.9	398	1.2	356
40	1063	KANAMMA/F/59	12.5	515	1.3	398
41	1154	CHANDRKALA/F/63	12.4	510	1.3	491
42	1266	PAVAI/F/66	12.5	514	1.2	492
43	1163	ANJALAKSHMI/F/61	12.7	399	1.1	476
44	1144	THANGAMMAL/F/64	11.9	436	1.0	348
45	1143	LALITHA/F/55	12.1	515	1.2	494
46	1188	KOKILA/F/58	12.8	398	1.2	348
47	1163	MARIAMMAL/F/59	12.7	377	1.2	487
48	1108	CHANDRA/F/54	12.6	379	1.0	367
49	1009	JAYA/F/56	12.4	510	1.3	389
50	1005	MARIAMMA/F/54	12.3	512	1.3	490

Legend : METS- Total Work load in Metabolic Equivalents,EX.DUR.-Total Exercise Duration in seconds,MAX.ST↓-Maximum Tsegment depression,TIME TO ONSET OF ST↓-Time to onset of ST segment depression in seconds,TIME TO OFFSET OF ST↓-Time to offset of ST segment depression in seconds.

3.CAG DATA – STUDY GROUP (I)

SERIAL NO :	CAG NO :	NAME/SEX/AGE	LAD / 1.7 Frames	LCX frames	RCA frames
1	757/05	BABU/M/62	46	25	35
2	761/06	PALANI/M/57	56	38	30
3	770/05	SESHADRI/M/59	57	41	30
4	778/05	PARASU/M/48	49	25	24
5	784/05	BASHA/M/52	24	41	31
6	786/05	LEELA/F/55	51	37	33
7	416/06	ELUMALAI/M/59	54	25	24
8	453/06	RAJI/F/62	56	25	24
9	480/06	ROSY/F/62	56	38	34
10	694/06	PREMALATHA/F/67	53	25	24
11	777/06	THANGARAJ/M/66	24	41	32
12	796/05	CHELLAM/M/39	24	38	33
13	799/05	VADIVAMMAL/F/42	48	41	31
14	810/05	SARAVANAN/M/46	54	39	32
15	816/05	PERUMAL/M/62	56	38	33
16	817/05	NAGAMALAR/F/59	55	25	24
17	711//06	SHAHUL/M/53	24	41	31
18	569/06	PATHUMA/F/53	24	25	31
19	819/06	NAWAB/M/55	56	25	24
20	869/05	YAKOUB/M/35	24	40	32
21	75/05	MANOHARAN/M/47	55	25	24
22	866/05	SRINIVASAN/M/45	24	38	32
23	872/05	SIVARAMAN/M/48	49	25	24
24	881/05	GOVINDASAMY/M/52	51	25	24
25	888/05	KISHORE/M/62	24	35	24
26	895/05	ABDUL AZIZ/M/55	50	25	24
27	906/05	SHABAN/M/61	51	25	24
28	929/05	CHITTI BABAU/M/57	24	36	33
29	995/05	SELVAM/M/58	54	25	24
30	934/05	SELVAKUMAR/M/56	48	25	24
31	949/05	MURUGAN/M/55	52	25	24
32	959/05	ROBERT/M/48	51	24	24
33	975/05	MASIMA/F/61	24	37	31
34	28/05	SAVITHA/F/49	48	24	24
35	36/05	CHANDRA/F/53	24	38	32

36	75/05	MANOHARAN/M/54	24	37	33	
37	83/05	MOHAN/M/63	50	24	24	
38	980/05	GOVIND REDY/M/55	24	36	31	
39	10/05	CHINATHAMBY/M/53	53	24	23	
40	119/05	SAROJA/F/54	55	25	24	
41	339/05	JAYA/F/49	56	25	24	
42	267/05	LAKSHMI/F/37	24	34	33	
43	171/05	DEVAKI/F/38	54	24	22	
44	110/05	MAHENDRAN/M/42	48	25	31	
45	136/05	VEERAMAL/F/48	49	25	31	
46	156/05	KANAGARAJ/M/46	52	39	32	
47	181/05	RANGASAMY/M/49	24	24	32	
48	230/05	ARUMUGAM/M/52	54	38	32	
49	232/05	SANKAR/M/59	24	37	31	
50	250/05	KANI/M/58	57	39	33	
51	264/05	MOHIDEEN/M/56	55	38	24	
52	274/05	KRISHNAN/M/48	52	24	33	
53	309/05	VASANTH/M/39	23	40	30	
54	367/05	RAJ MOHAN/M/36	49	40	34	
55	408/05	ASOKAN/M/38	24	35	31	
56	886/06	GEORGE/M/42	56	33	34	
57	943/06	HARI/M/49	24	38	32	

Legend : LAD / 1.7 – CTFC of LAD, mCTFC – mean CTFC of LAD/1.7,LCX and RCA

CAG DATA – CONTROL GROUP (II)

SERIAL NO :	CAG NO :	NAME/SEX/AGE	LAD / 1.7 Frames	LCX frames	RCA frames
1	762/06	RAJAMMAL/F/64	20	20	18
2	766/05	RAVI/M/68	24	25	24
3	765/05	RAMALINGAM/M/69	22	21	19
4	771/05	MANICK/M/42	22	22	21
5	772/05	RAGUNATHAN/M/41	23	23	22
6	773/05	MAHADEVI/F/46	20	22	24
7	782/05	SITHALAKSHMI/F/52	23	24	23
8	336/05	KUPPAN/M/58	24	25	23
9	433/05	RAMAKRISHNAN/M/58	21	25	21
10	437/05	DEVADAN/M/48	21	22	20
11	692/05	SURESH/M/47	24	21	19
12	699/05	JAYACHANDRAN/M/56	22	25	18
13	823/05	USHA/F/54	21	20	24
14	826/05	RAMASAMY/M/53	23	21	20
15	829/05	MANOHARAN/M/58	21	22	24
16	841/05	VISALAKSHI/F/59	22	22	23
17	845/05	RAJALAKSHMI/F/65	24	24	22
18	903/05	VEERARAJAN/M/66	21	23	21
19	923/05	RAGAVAN/M/62	22	23	22
20	930/05	MOHAN/M/48	23	24	24
21	966/05	SUBRAMANI/M/59	23	21	23
22	18/05	SATHYAMURTHY/M/68	23	20	23
23	998/05	SYED/M/69	21	25	24

24	1007/05	MOHD.IQBAL/M/64	23	23	19
25	64/05	MURUGAN/M/58	24	25	22
26	72/05	DHANDAYUDHAM/M/55	22	24	21
27	95/05	GOWRI/F/54	22	24	20
28	96/05	RAJESH/M/53	22	22	21
29	115/05	VEERASAMY/M/54	22	21	23
30	150/05	SAROJA DEVI/F/56	22	21	23
31	165/05	GAYATHRI/F/58	21	22	24
32	169/05	CHITHRA/F/48	21	24	21
33	187/05	BACKYAM/F/47	21	23	20
34	432/05	DEIVANI/F/52	23	24	21
35	287/05	RANI/F/53	23	25	22
36	318/05	GOWRI/F/61	23	25	24
37	330/05	KALYANI/F/60	22	22	23
38	386/05	SARASWATHY/F/62	21	24	22
39	442/05	MARIAM/F/58	21	23	24
40	64/05	KANAMMA/F/59	23	23	23
41	984/06	CHANDRAKALA/F/63	22	24	22
42	1047/06	PAVAI/F/66	22	21	21
43	1082/06	ANJALAKSHI/F/61	23	23	22
44	18/06	THANGAMMAL/F/64	24	22	21
45	97/06	LALITHA/F/55	23	23	20
46	265/06	KOKILA/F/58	23	24	19
47	902/06	MARIAMMAL/F/59	22	25	20
48	1011/06	CHANDRA/F/54	24	24	21
49	237/06	JAYA/F/56	22	22	22
50	35/06	MARIAMMA/F/54	24	23	21

Legend : LAD / 1.7 – CTFC of LAD, mCTFC – mean CTFC of LAD/1.7,LCX and RCA

4. FOLLOW-UP DATA – STUDY GROUP (I)

SERIAL NO:	NAME/SEX/AGE	ANGINAL EPISODE	HOSPITALIZATION FO
1	BABU/M/62	Y	Y
2	PALANI/M/57	Y	N
3	SESHADRI/M/59	Y	N
4	PARASU/M/48	Y	N
5	BASHA/M/52	N	N
6	LEELA/F/55	Y	N
7	ELUMALAI/M/59	N	N
8	RAJI/F/62	N	N
9	ROSY/F/64	N	N
10	PREMALATHA/F/67	N	Y

11	THANGARAJ/M/66	N	N
12	CHELLAM/M/39	N	Y
13	VADIAMMAL/F/42	N	N
14	SARAVANAN/M/46	N	N
15	PERUMAL/M/62	N	N
16	NAGAMALAR/F59	N	N
17	SHAHUL/M/53	Y	N
18	PATHUMA/F/53	Y	N
19	NAWAB/M/55	Y	N
20	YAKOUB/M/35	N	Y
21	MANOHARAN/M/47	N	N
22	SRINIVASAN/M/45	N	N
23	SIVARAMAN/M/48	N	N
24	GOVINDASAMY/M/52	Y	N
25	KISHORE/M/62	Y	N
26	ABDUL AZIZ/M/55	Y	N
27	SHABAN/M/61	Y	N
28	CHITTI BABU/M/57	Y	N
29	SELVAM/M/58	N	N
30	SELVAKUMAR/M/56	Y	N
31	MURUGAN/M/55	Y	N
32	ROBERT/M/48	Y	N
33	MASIMA/F/61	N	N
34	SAVITHA/F/49	Y	N
35	CHANDRA/F/53	N	N
36	MANOHARAN/M/54	Y	N
37	MOHAN/M/63	N	N
38	GOVIND REDY/M/55	N	N
39	CHINATHAMBY/M/53	Y	N
40	SAROJA/F/54	N	N
41	JAYA/F/49	N	N
42	LAKSHMI/F/37	Y	N
43	DEVAKI/F/38	N	N
44	MAHENDRAN/M/42	N	N
45	VEERAMAL/F/48	Y	N
46	KANAGARAJ/M/46	Y	N
47	RANGASAMY/M/49	N	N
48	ARUMUGAM/M/52	Y	N
49	SANKAR/M/59	N	N
50	KANI/M/58	Y	N
51	MOHIDEEN/M/56	N	N
52	KRISHNAN/M/48	Y	N
53	VASANTH/M/39	N	N
54	RAJ MOHAN/M/36	Y	N
55	ASOKAN/M/38	N	N
56	GEORGE/M/42	N	N
57	HARI/M/49	N	N

Y – PRESENT,N – ABSENT

FOLLOW-UP DATA – CONTROL GROUP (II)

SERIAL NO :	NAME/SEX/AGE	ANGINAL EPISODE	HOSPITALIZATION FOR AI
1	RAJAMMAL/F/64	N	N
2	RAVI/M/68	Y	N
3	RAMALINGAM/M/69	N	N
4	MANICK/M/42	N	N
5	RAGUNATHAN/M/41	N	Y
6	MAHADEVI/F/46	N	N
7	SETHALAKSHMI/F/52	N	N
8	KUPPAN/M/53	Y	N
9	RAMAKRISHNAN/M/58	Y	N
10	DEVADAN/M/48	N	N
11	SURESH/M/47	N	Y
12	JAYACHANDRAN/M/56	Y	N
13	USHA/F/54	Y	N
14	RAMASAMY/M/53	N	N
15	MANOHARAN/M/58	Y	N
16	VISALAKSHI/F/59	Y	N
17	RAJALAKSHMI/F/65	N	N
18	VEERARAJAN/M/66	N	N
19	RAGAVAN/M/62	Y	N
20	MOHAN/M/48	N	N
21	SUBRAMANI/M/59	Y	N
22	SATHYAMURTHY/M/68	N	N
23	SYED/M/69	Y	N
24	MOHD.IQBAL/M/64	N	N
25	MURUGAN/M/58	Y	N
26	DHANDAYUDHAM/M/55	N	N
27	GOWRI/F/54	N	N
28	RAJESH/M/53	Y	N
29	VEERASAMY/M/54	Y	N
30	SAROJADEVI/F/56	N	N
31	GAYATHRI/F/58	Y	N
32	CHITHRA/F/48	N	N
33	BACKYAM/F/47	N	N
34	DEIVANI/F/52	N	N
35	RANI/F/53	N	N
36	GOWRI/F/61	N	N
37	KALYANI/F/60	N	N
38	SARASWATHY/F/62	Y	N
39	MARIAM/F/58	N	N
40	KANAMMA/F/59	N	N
41	CHANDRAKALA/F/63	N	N
42	PAVAI/F/66	N	N
43	ANJALAKSHMI/F/61	N	N
44	THANGAMMAL/F/64	N	N
45	LALITHA/F/55	N	N
46	KOKILA/F/58	N	N
47	MARIAMMAL/F/59	N	N
48	CHANDRA/F/54	N	N

49	JAYA/F/56	N	N
50	MARIAMMA/F/54	N	N

Y – PRESENT,N - ABSENT